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# MYXŒDEMA, CRETINISM

AND THE

# GOITRES.

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MYXŒDEMA IN THE MALE. (Savill.)

*Taken from the Medical Society's Transactions, vol. xiii.*

*Printed from process blocks by* J. BALE & SONS, *London.*

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# MYXŒDEMA,

## CRETINISM AND THE GOITRES

*With some of their Relations.*

BY

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"The very nerves and sinews of knowledge consist in believing nothing rashly."

EPICHARMUS, *circ. Cent. XV. B.C.*

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# PREFACE.

The reader will soon find that the burden of this book is the septic or the infective nature of disease.

The points which more particularly I seek to establish are :—

(1) That Graves' disease in woman is an autotoxis, most frequently caused by the absorption of purulent products; that process being *aided*, rather than *induced*, by the toxines of terror or shock.

(2) The same products lead to the production of rheumatism in males, by acting in the same locality, viz., the medulla oblongata.

(3) If these products abolish the functions of the thyroid, we may get myxœdema.

(4) If these products invade the cortex, in large quantity and abruptly, we get a psychosis, as for example, mania; or some neurosis, such as epilepsy.

(5) If the invasion be more gradual and the poisons be more diluted, we get chorea.

Much of this of course is hypothetic, and is by way of being a provisional pathology.

Nothing, in scientific matters, least of all in pathology, can be viewed as final or absolute.

Nevertheless, it is along these lines that the campaign probably will be pushed.

It is difficult to avoid misconstruction as to the views of others. However, to escape at least one source of blunder, wherever such a course was possible, I have submitted pooofs for the correction of each contributor to our knowledge of these all-important subjects.

Where I have fallen into error, I shall esteem it a great favour if any reader will indicate an inaccuracy.

To Dr. Barnes I am indebted for the most useful part of this book. I refer to the excellent indices to be found at the end of the work.

I take this opportunity of thanking my printer for the trouble he has taken in producing this work, Mr. Danielsson for his careful and excellent reproductions, and many medical friends for valued criticisms.

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# MYXŒDEMA, CRETINISM AND THE GOITRES.

## CHAPTER I.

### Myxœdema.

Myxœdema, common in the northern parts of Great Britain, is rare in the United States. It is rare, too, in Germany, where acromegaly is comparatively common. Whilst the changes involved are evidently trophic in character, there are probably atmospheric or telluric conditions which determine distribution. It was recognised many years ago by the father of Dr. Byrom Bramwell, but was not definitely described as a distinct disease till 1873. The first clear account was given by Sir William Gull, in the *Transactions of the Clinical Society*, vol. vii., p. 180.

The name "myxœdema" was given to this disease by Dr. Ord. Though destined now to be immortal, this piece of nomenclature is not above criticism, for on the one hand, the disorder is not associated with a true œdema, and on the other, there is by no means always an excess of mucin in the tissues. This has been definitely shown by Halliburton, p. 90, vol. i., *Journal of Pathology and Bacteriology*. It was observed by Victor Horsley, that in one case of athyrea, the parotid secretion, which normally contains no mucin, was found to be rich in that material.

More common in women than in men, in the proportion of 6 to 1, it is most common during the epoch of childbearing. Pregnancy has been known to arrest the progress of the disease, which however returns after the birth of the child. This occurred in one person three times in seven years. See Report of Myxœdema Committee, supp. to vol. xxi. of *Proceedings of Clinical Society* p. 181, 1883.

Mucin is found to be in excess in cases of *acute* experi-

mental myxœdema, whilst it is usually absent in chronic experimental myxœdema.

That the septic and infective invasions connected with child-bearing predispose to the disease, is shown by the interesting table of Hun and Prudden. Sixty-four myxœdematous women had had over three hundred children and twenty-nine miscarriages.

Myxœdema occurs at all ages, and in both sexes. It occurs in the male, as in the following case,[1] but it is most frequent in women between the ages of 30 and 65. It is especially common at the menopause. Several members of one family are sometimes afflicted.

### Case 1.

*Myxœdema in the Male.*
*(See Frontispiece.)*

J. Taviner, age 45, was admitted into the Paddington Infirmary, under the care of Dr. Savill, on Nov. 1, 1888. His symptoms commenced about eight years before with weakness, puffiness of the skin, first in the forehead and eyelids, then in the feet, and a tendency to feel the cold very much. The family history shows great longevity in his ancestors, and he has a healthy family of three. There is nothing of importance in the previous history, except that he used to drink beer and spirits heavily ; no history of syphilis.

His condition when admitted was very typical of the disease. The following note was made:—He is a finely formed man, with a chest measurement of 40 inches ; the face looks swollen, especially round the eyes, nose and cheeks ; the lips are thickened ; the skin is very dry and somewhat wrinkled ; the hair on the scalp and face is scanty, wiry, and brittle. The expression of his countenance is dull and placid, and there is a pink flush on the nose and on each cheek. The skin of the extremities is very dry and scurfy, while the hands are flat and "spade-like." In both supraclavicular regions there is a distinct fulness. The thyroid cannot be felt.

[1] For the excellent coloured illustration, and for the details of the case, which was read before the Medical Society, I am indebted to Dr. Savill.

During the period of four and a half months that he was under observation, the following points were noticed :—His temperature was subnormal (average between 97° and 98°), and he seemed to feel the cold very much; he complained of sensations "like a trickling of cold water down the back," and was never happy unless in bed or near the fire. There was no impairment of sensation, but the superficial and deep reflexes were both much diminished. There was general loss of muscular power, and very decided slowness of movement. With regard to his intellectual processes, the characteristic slowness of speech and thought was most marked, but his intelligence was fair, and he had no delusions, no abnormal persistence of thought. Memory was impaired, and he was often irritable, resenting any interference. His eyesight was very good; but he suffered from lachrymation, and the pupils reacted sluggishly to light and accommodation; his hearing had been impaired for twelve years. Other special senses were normal. The urine never contained any albumen. The amount of urea excreted during twenty-four hours was estimated on two occasions, and found to be 373 grains and 260 grains respectively; the average specific gravity was 1·012. His other organs were perfectly normal.

The patient remained in the Infirmary till March 23, 1889. No special treatment beyond the administration of tonics and the regulation of the digestive system was carried out, and his condition was not materially altered when he left. This example shows well the uninteresting face, the loss of hair, and the thickened skin, so typical of the disease. The broad flat hand, too, is very characteristic.

Myxœdema is, in its onset, usually slow and insidious, and whilst the development is gradual the course is slow and chronic in a general way; nevertheless acute and sudden invasions are not quite unknown. The first symptoms are lassitude and skin dryness, with increased susceptibility to cold. It will be remembered that in exophthalmos and acromegaly there is a tendency to excessive sweat, and a consequent minimising of electrical resistance, the reverse being the case

in myxœdema, owing to the dryness of the skin. Myxœdema is usually associated with absence—or else atrophy—of the thyroid gland. The causes of the atrophy are at present quite unknown.

Fibrous degeneration of the thyroid has followed pressure on the inferior laryngeal nerve in two subjects of aortic aneurysm of specific origin. Hale White has suggested that the inferior laryngeal is the trophic nerve of the thyroid gland.

When the disease is fully developed, the physiognomy undergoes a most marked change, those who suffer from this disorder get to present a strong family likeness to one another, the features become coarse and broad, assuming a placid and mask-like form of expression. The eyebrows are elevated, probably to counteract the tendency to ptosis, the lids puffy, the eyes are almost closed, the eye-ball is barely seen through a narrow fissure. The lips are large, thick, and livid; the lower lip being everted and pendulous, as in leprosy. The skin of the face is often affected with chloasma; it is sometimes yellow and sometimes mahogany-like in colour. The cheeks show usually a well-defined central patch of vivid tint, contrasting strongly with the marked pallor of the lids.

Though hebetude is the rule, some patients are very irritable in disposition. Anæmia, associated with increased leucocytosis, is usually present.

Tubercle is often associated with myxœdema. Alcoholism and syphilis do not appear to predispose to it. The tendency to it diminishes with age. The case that follows is an interesting example of how late in life it may come.

The next illustration, for the use of which I am indebted to Dr. W. Tusting Cocking, of Sheffield, forms an excellent example of the beneficial effect of thyroid feeding, even when commenced in advanced life.

### Case 2.

### *Myxœdema in Advanced Life.*

The subject is an infirmary patient, admitted on January 19, 1893. Had had a hard and laborious life, having been twice married, and had borne ten children.

Dr. Cocking's Case of Myxœdema in Advanced Life. Aged 68.

The details may be found in the *Sheffield Medical Journal*, vol. i., p. 312.

She had complained of loss of hair during about four years, there were also weakness, vertigo, general sense of coldness, diffused swelling and œdema of the ankles, with difficult speech. No mental decay, lungs healthy, heart sounds weak, but otherwise normal; temperature, 97·4°; urine 38 oz., 1017, acid, no albumen.

The extract of half a gland was given, temperature rising suddenly to 103° F. It fell abruptly in two days. After February, half a raw gland was given finely minced, with the same effect. Later, the same dose was given on alternate days, then twice a week. The photograph was taken in May.

The first manifest effect was exerted upon the skin, which after three or four doses, became quite moist and supple. It has continued to act freely ever since.

With the exception of an occasional slight puffiness of the lower lids, there is now no swelling of the face; the expression, too, has considerably improved.

She feels better and brighter in every respect, and has lost the sensations of light-headedness and chilliness.

She is considerably stronger, being able to walk up and downstairs and in the infirmary grounds with ease. The very scanty old hair has grown considerably. It falls out much less readily than before, whilst the scalp is now covered in addition with a new soft, silky growth, three or four inches in length. Her speech is less slow, the inter-syllabic pauses are less marked; indeed they are now scarcely noticeable. The temperature which, during the first three months of treatment, ranged between 98° and 100°, has, since the diminution of the dose, been practically normal. The pulse is stronger than it was, it is somewhat rapid at times, but no definite relation can be detected between its frequency and the quantity of gland administered. There has been no appreciable alteration in the amount of urine during the treatment. Two attacks of syncope occurred after exertion. They quickly subsided after the administration of stimulants. Dr. Murray and others have insisted on the necessity of exercising great

caution in the management of patients having cardiac feebleness.

This example certainly exemplifies the importance of great care in cases of cardiac asthenia.

The memory for recent events is said to be impaired; this is probably due to a want of attention, as Kesteven[1] has pointed out with regard to old age. The special senses are impaired and the brain loses its needful and constant stimulus, reflex peripheric impressions. The mental disorders are peculiar and characteristic. Acute mania has occurred in the early stages. Melancholia and dementia are common, but there is no incoherency, and delusions are absent. Headache in the earlier stages is a common feature, it may be either frontal or occipital. The vocal cords are swollen and thickened. From the tone of voice and from the manner of utterance alone, the disease may be diagnosed. The speech is very typical; it is slow, monotonous, and deliberate. There is sometimes so much persistence in idea that great difficulty is found in changing the subject or in terminating the conversation. Sensation is usually retarded; hearing, smell, and taste may be impaired or perverted. The teeth decay, become loose, or break off. The gums are usually swollen and spongy. The tongue is enlarged and protruding from the mouth. The uvula and the soft palate are swollen. Hæmorrhages from the mouth, nose, throat, and uterus are not uncommon. Dysphagia is present in some cases, and occasionally there is regurgitation of food and of drink. The belly is pendulous; hypertrophy of the uterine neck has been reported by Victor Corbould. As myxœdema is prone to follow Graves' disease, and as Graves' disease may occur as a result of chronic cervical catarrh, of which one result is hypertrophy of the cervix, this is not to be wondered at.

The skin is thickened, dry, scaly, bran-like, and downless. The entire body is swollen, as if the subject were

[1] "On a Spreading Variety of Nerve Dulness," by W. Henry Kesteven, M.R.C.S., *The Lancet*, Dec. 9, 1893, p. 1435.

affected with acute œdema; but pathological investigation has shown that the effusion is limited to the superficial layers of the corium, and fluid does not exude on puncture. In some cases, and in the later stages, true œdema may appear, especially in the ankles. The secretions of the sebaceous follicles and of the sweat glands are usually absent. Cutaneous sensibility is impaired, but it is general, not confined to nerve areas as in leprosy, nor is it absolutely lost, as in the latter disease.

There is swelling of the epithelium lining the tubes of the sweat and sebaceous glands, with obliteration of the lumina; and there is nucleated fibrous growth in the surrounding tissues. The hair is dry and crisp, it becomes scanty, not only over the scalp, but also on the brows, the axillæ, and the pubes. The hair follicles atrophy; often there is extensive deposit of pigment in the skin. Warts are common. The epidermis becomes thin in some cases, in others there are areas of dense fibrous overgrowth. There is a characteristic enlargement and swelling of the hands. The nails are affected. They become dry, lustreless, brittle, and cracked. The subcutaneous tissue is swollen; this is most marked in the extremities, it presents the appearance of œdema, *but there is no pitting on pressure.* Fulness of the supraclavicular region is usually present. This is also very noticeable in some cases of sporadic cretinism.

Morvan observed that whilst the functions of the skin are arrested, the other emunctories are often more active than usual. Thus, the salivary glands, the mucous follicles of the nose and mouth, and the lachrymal glands secrete more freely than usual. (*Gazette Hebdomadaire*, p. 543, August 21, 1881.)

There is no change in the nervous system, except in the peripheral nerves, in which there are frequently indications of a chronic neuritis. The lymphatic glands and the adrenals are usually normal.

There are joint pains, and owing to paresis of certain muscles, movements are clumsy, the gait waddling and ungainly.

There is frequently a certain amount of incoördination,

the legs are prone to give way unexpectedly. Sometimes the patient suffers from cramps.

The heart-action is feeble and muffled. The average pulse is 70, infrequent, with low tension.

The breathing is slow ; dyspnœa is frequently complained of, but there is no change in the organs of respiration ; this is quite characteristic of myxœdema.

Professor Greenfield has laid stress upon the altered reaction of myxœdematous cases to tubercular invasion. There is a marked proclivity to pulmonary phthisis, yet its manifestations are modified in a most marked manner.

Professor Greenfield's cases were characterised by their rapid course and by the absence of the ordinary symptoms.

The temperature of the myxœdematous is below normal, and the symptoms are greatly aggravated by a low temperature. The patient objects even to a cold drink.

In the kidneys there are found occasionally, swelling and pallor, due to the presence of myxomatous degeneration around the arteries at their division, and an extension of a cellular infiltration between the tubules in that position, whilst the cortex is normal.

The urine is of low specific gravity, hyaline and granular casts may be seen, and albumin is often present. There is occasionally decided cystic irritability.

In the *International Journal of the Medical Sciences* for August, 1888, p. 140, Hun and Prudden recorded polyuria. They found albuminuria present in twenty per cent. of their cases. Sometimes there is free uric acid. The kidneys were said to be normal in one-third of the cases collected by the Clinical Society Committee, probably most cases suffer from some amount of renal cirrhosis before they terminate.

The characteristic morbid changes found after death are few. As a rule, fat is abundant at the ordinary points of distribution.

Passive effusions into the serous cavities, and slight general anasarca are not infrequent.

In the thyroid gland itself, there is in the earlier stages a small celled infiltration of the walls of the vesicles, accompanied or followed by epithelial proliferation in their interior. In the latter stages, the gland becomes converted into a

delicate fibrous tissue, in which the remains of the vesicles are represented by groups of small round cells.

The course of the disease is, as we have said, steadily progressive, although in some cases periods of remission have been noted. In one case, this disorder is said to have disappeared during two successive pregnancies, and in one other instance, the symptoms diminished under similar circumstances. If these cases be accurately recorded they are of the highest interest. They at once suggest that either the toxines produced in the fœtus or in the mother, have an action resembling that of thyroidine, or else that the fœtal thyroidine passes unchanged into the maternal circulation.

As a rule, whilst life lasts, it is a burden. Many of the patients end their days in an asylum. Dr. Starr, speaking on the subject before the New York Academy of Medicine, on November 16, 1893, made the following important observations:—The great importance of this phase of the question is, that there are undoubtedly many people confined in lunatic asylums, who are actually afflicted with myxœdema, of which the mental disorder is a prominent characteristic, and who might be cured in three months by the use of the extract. He could speak on this subject from personal experience, for he had had three patients under his care for three years, without recognising their true character. It seems a pity that all alienists are not as courageous as Dr. Starr. Superintendents of asylums would certainly do well to look over their patients, and see whether they had made similar mistakes.

For an interesting sketch of the earliest notices of myxœdema, the student may consult Dr. Byrom Bramwell's brief but excellent monograph, which forms the first part of the "Atlas of Clinical Medicine," vol. i., 1892.

By far the most complete account of the disease which has yet appeared, was published in 1888. It is the report of a committee of the Clinical Society of London, under the presidency of Dr. William Miller Ord, to whom we are indebted, not only for the name by which the disease is now universally designated, but also for a great deal of what is known of its symptoms and of its pathology.

This report practically proved the identity of myxœdema, sporadic cretinism, and the condition called by Kocher of Berne, "cachexia strumipriva," which has been observed to develop after total extirpation of the thyroid gland. It will necessarily rank as the standard work of reference on the subject for many years to come. Dr. Ord's first observations were made in 1861.

His first complete recorded notes of this disease were published in the *Transactions of the Medico-Chirurgical Society* at p. 71 of the sixty-first volume for the year 1877.

To Dr. Hector Mackenzie I am indebted for many of the preceding facts. His description of the steps by which the success of the thyroidine treatment was established, is so graphic and interesting, that I am tempted to reproduce it at length.

"In regard to treatment, at the time of the Clinical Society's report little could be done to alleviate the disease, little or nothing to check its progress. Tonics, jaborandi and nitro-glycerine were given to improve the appetite and to act upon the skin, and were reported to have produced temporary benefit. For such patients as could afford it, migration to warmer climates during the winter was strongly recommended. But the labours of Dr. Ord, Professor Horsley, Dr. Semon and others had brought the knowledge of the disease to such a pitch that a cure for it was not long wanting. Dr. Ord in his original communications on the subject had called special attention to the atrophic condition of the thyroid gland. Dr. Semon, struck by the resemblance of the train of symptoms observed by Kocher to follow after complete thyroidectomy, had first brought the matter forward in this country, and by indefatigable energy was principally instrumental in collecting the vast amount of evidence tending to prove the identity of this cachexia with myxœdema. Professor Horsley, by numerous laborious experiments, showed the close resemblance of the dyscrasia, produced in some of the lower animals by the removal of the thyroid gland, to human myxœdema. The result of these investigations amounted to a proof that the one thing lacking in the myxœdematous condition was a functionally active thyroid

gland. Professor Schiff and others after him had shown that the evil effects of thyroidectomy in animals could be diminished by transplanting a thyroid gland previously to the operation. This important observation Professor Horsley followed up by suggesting a similar procedure as a possible means of arresting the progress of myxœdema. This suggestion was accordingly soon carried into execution, and the operation was attended with striking, but unfortunately, only very limited and temporary improvement. The difficulty was to effect the survival of the transplanted gland in its new position and what actually happened was its absorption by the surrounding tissues. The fact of improvement at all was, however, encouraging. The benefit resulted so soon after the operation that it could be explained only by the absorption of some substance actually present in the gland at the time of transplantation. I have not seen any explanation of the curious fact of the great amelioration of the disease during pregnancy to which I have already alluded; and it seems to me likely that the thyroid of the fœtus supplied for a time the place of that of the mother, the benefit naturally terminating with delivery.

The next step was the employment of hypodermic injections of a glycerine extract prepared from thyroid glands, first in animals after thyroidectomy, and secondly in myxœdema. The fact of its usefulness in animals, with which the names of Vassale and Gley are associated, suggested to Brown-Séquard and d'Arsonval its probable utility in myxœdema; but, apparently quite independently, the idea of its use seems to have occurred to Dr. George Murray of Newcastle, who was amongst the first, if not actually the first, to employ this mode of treatment, and certainly the first to prove its success.[1] By Dr. Murray's method very

[1] Dr. Geo. R. Murray, of Newcastle, first suggested Thyroid Extract as the remedy for myxœdema in February, 1891. A report of this appeared in the *British Medical Journal* of March 14, 1891. at p. 586.

Dr. Murray first actually carried out the treatment on April 13, 1891. The results were described at the July meeting of the British Medical Association of the same year. *The method, therefore, is English in origin,* for Brown-Séquard and d'Arsonval first published their *suggestion* in the *Archives de Physiologie* for July, 1891, three months after the remedy had been actually *used* in England.

Reference however to the letter of Mr. Hurry Fenwick, reprinted in the Appendix, makes it clear that as early as 1890, the idea of the hypodermic use of thyrodine had already occurred to at least one other mind.

beneficial results were soon obtained by other physicians, and numerous reports of cases successfully treated by it appeared in the medical journals, and in the transactions of the medical societies. But, excellent as these results were, the method was not altogether free from objection. Some sensitive patients shrank from the hypodermic needle. Unless the fluid used for injection was absolutely sterile, subcutaneous abscesses and indurated swellings were apt to follow the injections. It was also found that rather alarming symptoms, such as lividity, pain, loss of consciousness, temporary loss of power in the extremities or general muscular spasm, sometimes supervened during or immediately after the administration of the injection. The difficulty with which the physician had to contend when he prepared the extract himself has been removed, and the risk of the occurrence of septic abscesses has been greatly lessened by the enterprise of Messrs. Brady and Martin of Newcastle, who now prepare weekly a sterilised extract which they supply at a moderate cost, considering the care required in its preparation. Putting the risk of local effects aside, however, I cannot but consider that even the rare occurrence of such unpleasant symptoms, as I have mentioned, is a serious drawback when a long series of injections has to be taken into account.

The next advance, and a very important one, is closely connected with the patient who is here to-day, to all intents and purposes cured of myxœdema. This was the discovery which I made that the administration by the mouth of the thyroid gland or of a preparation derived from it served the same purpose as hypodermic injections of thyroid extract—in fact, had all its advantages without any of its disadvantages. By a curious coincidence the same discovery was made about the same time, quite independently, by Dr. E. L. Fox, of Plymouth, and an account of his case appeared simultaneously with that of mine." [1] (Clinical Lecture, delivered by Dr. Hector Mackenzie, at the Royal Free Hospital, reported in *Lancet*, January 21, 1893.)

It is probable that all the bad effects which sometimes follow the use of thyroidine, may be easily avoided by using it

[1] *British Medical Journal*, October 29, 1892.

as an inunction. When thyroid extract cannot be tolerated if administered by the mouth, I should strongly recommend a trial to be given to the endermic method, which is conducted in the following way : twice a day, after hot sponging and vigorous towelling, the body is well rubbed all over with a mixture of thyroidine gr. x.; ether ʒi.; lanoline ʒj. The gray preparations of thyroid extract are the best. I first administered thyroidine by rubbing it into the skin on June 9, 1894.

Dr. Charles Forbes, in the issue of the *Medical Times and Hospital Gazette* for March 3, 1894, makes the suggestion that thyroid feeding be tried in the following conditions : viz., acromegaly, in the course of which the thyroid is often diseased, catalepsy and in old malarial dystrophies.

The diagnosis of myxœdema should not be difficult. There is but one disease with which it is likely to be confused, and that is chronic Bright's disease. There is no doubt that up to the time of its individual recognition, the earlier cases were called Bright's disease, and the later ones were arranged under differing forms of insanity. But in Bright's disease there is no bridge of hypertrophied tissue running to the nose. There is no drooping of the eyelids, with elevation of the brows, so typical a feature of myxœdema. In Bright's disease the skin fulness is most marked in the more dependent portions of the body; it is generally distributed in myxœdema. Whilst albumen is present in both disorders, it is more marked in Bright's disease, tending rather to increase towards the later stages of myxœdema and to diminish in morbus Brightii. The dysphagia, the loss of hair, the tone of the voice, the manner of speaking, and the mental symptoms, are characteristic of myxœdema; they are not likely to be confused with the group which goes to make up chronic renal degeneration.

There is an excellent historical account of myxœdema in the *American Journal of the Medical Sciences*, for May, 1894, at p. 515. The author is Dr. George W. Crary, of New York. I should like here to draw attention to a paper of extreme value on the synthesis of these morbid conditions, by Solomon Solis-Cohen, in the February issue of the same journal, entitled "Vaso-motor Ataxia."

## CHAPTER II.

### Cretinism.

When the myxœdematous tendency occurs in the young, it presents peculiar features. Its manifestation is then recognised as "sporadic cretinism."

Fodéré, who was himself goitrous, maintained, as early as the beginning of this century, that goitre was the first step towards cretinism. (See Robinson's "Thesis on Thyreocele," Churchill, 1885).

Sporadic cretinism was first described as a disease by Curling in 1850. The account may be found at p. 303, in the thirty-third volume of the *Transactions of the Medico-Chirurgical Society*.

The name sporadic cretinism was first used by Hilton Fagge, in the year 1871. To him is due the credit of first suggesting that "a wasting of the thyroid body might prove to be a constant character of the disease." His words are to be found enshrined in the proceedings of the same society, at p. 166 of vol. liv., during the year 1871. The resemblance between the symptoms of myxœdema and those of the "cachexia strumipriva" or "myxœdème opératoire," the result of the total ablation of the thyroid, established by Kocher, Victor Horsley and Felix Semon, amply confirmed the remarkable prediction of Hilton Fagge.

There is a good account of cretinism in the work of Bournville, entitled "Recherches sur L'Epilepsie, L'Hysterie et L'Idiotie" vol. x., p. 100. An excellent sketch appears by Byrom Bramwell at p. 17 of the "Atlas of Clinical Medicine."

In these cases there is either congenital absence or arrest of development of the thyroid gland. The child is dwarfed, rarely exceeding forty-two inches in height. The neck is

CRETINISM.
Before Thyroid Treatment.

CRETINISM.
After Thyroid Treatment.

thick, the extremities short and undeveloped. The abdomen is prominent: there is lordosis. The epiphyses are thickened, the skin is dense. There may be general alopecia, or the hair on the head may be thick and bushy, and hair may grow on the face. The face is large, the lips thick and the expression dull and vacuous, though the child may be made to smile. There is often great irritability of disposition, sometimes passing over the boundary line that separates ill-temper from insanity.

For the details of the next example, and for the use of the illustrations, I am indebted to the courtesy of Dr. Wallis Ord.

In this case, the improvement in general intelligence, which took place under the thyroid treatment, was exceedingly striking.

### Case 3.

*Sporadic Cretinism in a Girl.*

F. K., a female child, was admitted into the Victoria Hospital, Chelsea, in February, 1893. She was then 7 years of age. She was a typical cretin. She could not walk nor speak, had but little intelligence, no thyroid gland could be felt. She commenced the thyroid treatment on March 1. The second photograph shows her at the end of six months' treatment. She could then walk, with rather a tottering gait, she had gained markedly in intelligence and had increased considerably in height. The percentage of urea in her urine increased from ·4 before treatment to 3·5 after treatment. After the lapse of a year she can walk and run with ease; she can talk, not very distinctly as yet, but sufficiently clearly to make her wants known. She sings, with a very fair idea of tune; she is growing rapidly, and is cutting her second teeth. Her intellect is distinctly sharp and her memory good. She is still taking thyroid tablets. It is interesting to note that for the first few weeks of treatment she lost weight rapidly, then there followed a stationary period whilst for the last eight months she has been gaining

steadily. She has had no rise of temperature, and no symptom that could be attributed to the treatment, except that about Christmas last she began to exhibit great nervous irritability. The dose of the thyroid extract was then lessened and this condition more or less passed away. She still suffers from occasional attacks of passion. The improvement in her skin, hair and nails is remarkable. In fact, in this respect at the present time she is just like a normal child.

### Case 4.

*Sporadic Cretinism in a Boy.*

John Hibbins, aged 6½ years, was first brought to hospital on October 6, 1893. He was a native of Lincolnshire. There was no history of insanity or hereditary disease in his family. It was noticed at his birth that he was different from other children. When seen he could not walk or talk, but he could stand alone; he was good tempered, and had only just sufficient intelligence to be pleased with toys. He could not feed himself, was dirty in his habits, and was much affected by cold weather. His "facies" was typical, except that the skin was not so dry as usual, and that his hair was fairly abundant. No thyroid could be felt. There were marked supraclavicular masses. The urine contained 2 per cent. of urea, and no albumen.

Treatment by the administration of 5 grains daily of dry thyroid extract, was commenced on October 9. On October 11 and 12 the percentage of urea was respectively 2·4 and 2·6. He lost weight very rapidly, and became after a time so emaciated that the thyroid treatment had to be suspended, and cod liver oil was administered instead. On December 11 he contracted scarlet fever, and he was sent to the fever hospital, where he died on December 18. At the *post-mortem* examination signs of broncho-pneumonia and of acute nephritis were found. The thyroid was totally absent. The skull cap was thickened, and the cerebral ventricles

Cretinism in the Male.

rather dilated. For these careful notes, and for the cut that illustrates them, I am indebted to Dr. Wallis Ord.

Under thyroidine the skeleton enlarges and the general condition of the patient improves : *but it must be remembered that on cessation* of the treatment the symptoms recur.

That nutritional causes are involved in the production of goitre and cretinism is rendered probable by the fact that these two diseases were endemic in parts of the western counties, till the repeal of the corn laws first, and afterwards the agricultural strikes, improved the food supply. We can scarcely realise how short a time has elapsed since semi-starvation was the ordinary state of things in country districts. Under the influence of purer water, better food, healthier dwellings, and with minds less tortured by the perpetual terror of imminent starvation in this world, and of purgatory in the next, healthier children were begotten and cretinism entirely disappeared.[1] The appointment of rural sanitary inspectors is now making goitre itself a curiosity.

It has been stated that exiled Russians develop bronchocele in Siberia, whilst the native Siberian enjoys an immunity. If this be true there are many ways of explaining it. The expatriated Sclav is depressed in mind, unnourished in body; he occupies by preference small, overheated, and unventilated dwellings. The born Siberian lives in the open air. Compare these points with the prevalence of goitre in Switzerland. During the summer months, the picturesque châlet is too often a whited sepulchre. Whilst externally so fair to look upon, it is, alas! inside, a sink of unhygienic iniquity. In winter, when strangers rarely visit the Swiss at home, matters are far worse. The women and children rarely venture out. Their teeth are not cleansed, their secretions and excreta seldom properly removed. They rebreathe their own air. The reeking atmosphere is still further contaminated with the exhalations of the store beasts, which are often

[1] Read, writing in 1836, "On the Cause of Bronchocele," says that Chiselborough, in Somerset, then contained 350 inhabitants, most of them goitrous. Of these 24 were crétins.

accommodated, during the rigorous and inclement season, under a floor constructed with gaping boards. Added to this the water supply is far from faultless. A careful consideration of the geographical distribution of goitre, carefully noted in the classic work of Saint-Lager, "Du Crétinisme, et du Goitre Endemique," Baillière, Paris, with a glance at the excellent goitre map which accompanies the work of Dr. Heinrich Bircher, of Berne, "Der endemische Kropf," Schwabe, Basle, 1883, will serve to convince any man that there is no common geographical cause that can explain all kinds of goitres. James Berry, formerly Professor of Pathology at the Royal College of Surgeons, has contributed much valuable material to the literature of goitre. He has denied that insanitary surroundings have anything to do with the production of bronchocele. I am reminded by a medical friend from Hibernia that few things in the world are so unsavoury as an Irish bog-cabin. Well, I have been into several, and I entirely concur with his opinion. Yet he says that goitre is rare. Goitre is certainly not common in Ireland, but it is not unknown. The various forms were first clearly recognised by two Irish physicians: by Stokes first and then by Graves. It has been stated that goitre is unknown in Norway; a recent visit to that country convinced me of the erroneousness of that statement. The same thing is said of London. I find that is quite incorrect. Goitre is very common in London, but it is usually overlooked. If the thyroid enlarge downwards, then it does not do what French people call "jump to the eye"; it must be sought for during the act of deglutition.

A very large proportion of the patients, who seek assistance for chronic pelvic suppuration, have an enlargement of the thyroid body. This hypertrophy is often confined to one lobe, preferentially to the right, and *that* for developmental reasons, as pointed out by Fitzgerald.[1] Most frequently the isthmus alone is enlarged. This elective site would be enough to convince us that we have not to deal with a general hyperæmia, but with some cause that can act locally, as well as generally.

[1] "Theory of a Central Lesion in Exophthalmic Goitre," *Dub. Journ. of Med. Soc.*, March, April, 1883. Wm. A. Fitzgerald.

London has the finest food markets in the world and one of the worst of water supplies, and there is little doubt that these facts impress a certain peculiarity on its diseases.

Before entering on chapter iii. I must glance briefly at a matter of enormous importance, a matter which I venture to say has not received, at the hands of the profession, the amount of attention that it certainly merits.

Nearly a quarter of a century ago, Gautier in Paris, and Selmi in Bologna, showed that certain parts of the body perish and putrefy during life, in precisely the same manner, and with exactly the same products, as they do after death, the only difference being that during life these products of decay are removed as soon as they are formed, whilst, after death, they are not removed at all.

About the same time, in the year 1862, Thomas King Chambers, applying these facts clinically, presented to the profession a remarkable book, entitled "The Renewal of Life." In it he elaborated, and applied to the needs of practical medicine, the very curious paradox that life consists in perpetual death, and that the arrest of tissue-decay is destruction. This is, to-day, a mere truism, but when it appeared as a novelty, the medical world was greatly startled, not to say scandalised, by its unexpected advent. Though, to a large extent, unadmitted and unconscious, the influence of this book was enormous. It cast a new complexion on medical practice. Traces of its indirect effects are plainly visible to this day, in the sustaining and building-up views of many middle-aged physicians still living.

It is estimated that four-fifths of the katabolic products of the human body are burned away by means of oxygen. Hence the importance of fresh air, of vigorous breathing, and, therefore, of that systematic muscular exertion which lends a zest to respiration. But as the effete products are not all expelled aerially, for some are dependent on "water carriage" for their removal, we can see the necessity also of copious pure drinking water to wash away the *débris* of our dead selves. These particular methods of destruction, of tissues which are no longer needed, are technically known

as *aërobic* transformations. They may be viewed as "combustions." Interference with processes like these, with or without the intervention of certain microörganisms, leads to indigestion, gout, rheumatism, chorea, goitre, neurasthenia, skin disease, hysteria, neuralgia and mental alienation. In fact, this group includes most of those conditions which we are in the habit of calling "Chronic Functional Disorders." They rarely tend to destroy life abruptly.

The remaining one-fifth of retrograde, metamorphic material is formed at the expense of the actual tissues themselves. This disassimilation is independent of all demands on external oxygen. In other words, this fifth part of the tissues perishes by a putrefactive process, *anaërobically* in fact. When these latter ptomaines or so-called "animal" alkaloids and extractives are arrested in their downward career of degradation, they become at once the source of extremely urgent peril to life. Examples of these are familiar to us under the names of hospital gangrene, puerperal fever, uræmia and the so-called "zymotic" diseases.

We usually call these "Acute Diseases"; some of them are known as "the Acute Specific Diseases."

Quinquaud ("Animal Alkaloids," A. M. Brown, M.D., p. 158, second edition) has shown that the alkaloids cause a tendency to low temperature; a typical example of their action being the "cold" form of cholera. The extractives, on the other hand, are prone to induce high temperature, as in typhus, and enteric fever. Up to a certain point this high temperature is favourable, because it aids the process of phagocytosis. We can sometimes see these extremes of temperature alternate in their predominancy, thus explaining the abrupt variations seen in the course of the continued fevers. We can readily conceive of these two forms of toxine neutralising each other, when they chance to exist in equal quantities in the economy. Under such a condition grave illness may be present without corresponding change of temperature. Those agents which we introduce into the body under the name of remedies, when successful, probably act either by neutralising natural toxines existing in excess, or

by stimulating tissues which have been paralysed by toxines.

Careful provings of these metabolic materials have been made on healthy animals. Records of them may be found at page 49, of Dr. Brown's work on the "Animal Alkaloids," already referred to. Loss of muscular contractility is one of the most unvarying results. It is due to this action of the organic toxines, that the heart slowly fails in puerperal fever; and the diaphragm declines to descend in some fatal forms of diphtheria. It is in this way that the ptomaines conduct to death. When we have perfect provings, made by well-trained physiologists, of all the leucomaines, on healthy and intelligent men and women, then we shall hold in our hands the clue to a thousand pathological labyrinths.

To the younger members of our profession I commit this noble task. They may prepare themselves by mastering the works of the following authors: Bouchard, A. M. Brown, Victor Vaughan and Griffiths.

How, may we ask, are these terrible poisons eliminated during life? The glands of the human body are especially commissioned to play the part of scavengers.

In primitive unicellular organisms, such as the moneron and the amœba, one cell must undertake all kinds of katabolism. But the tendency of complex organisms is always towards the division of labour, so that in an advanced stage of physiological evolution, as in the higher mammals, special glands have slowly elaborated a selective function. That they will, if time be allowed, uneducate themselves is quite true. But, just as this painful process of selection has required countless ages for elaboration, so the element of time is a needful factor in the backward road of return, *ardua vestigia retrorsum.* This is one reason why the sudden removal of an important specialised gland is followed by death, whilst its gradual destruction will be tolerated and life may continue.

Attempts have been made to solve the problem of the utility of the thyroid body and of the adrenals, by the negative method of ablation. In rabbits, M. Gley has found that the removal of the thyroid body and of two small embryonic

bodies named "thyroid granules," usually leads to rapid death preceded by convulsions, though a few animals present, in the course of some months, a special form of cachexia resembling the myxœdema of man. It is curious that herbivores do not die after removal of the thyroid if kept warm. Dogs perish after two or three months: the carnivores generally die if artificial athyrea be performed. M. Langlois finds that excision of both adrenals occasions death in the course of twenty-four hours with loss of muscular power, dyspnœa, and sometimes convulsions; but if only one be removed, life is usually preserved, the animal becoming very thin. (*Lancet*, Dec. 30th, 1893., p. 1623.)

The liver, the spleen, the kidney, the intestinal glands and the adrenals appear to possess the property of turning out broken down blood-pigment. In diseases of these organs certain colouring matters are left in the circulation and they become irregularly deposited in the tissues. I say "deposited" though it would certainly be more accurate to put it thus: "the removal of unneeded pigment granules is arrested." These so-called "deposits" are chiefly made in areas under the control of certain nerves; notably of the musculo-spiral and of the fifth cranial pair, nerves especially exposed to traumatism and to abrupt transitions of temperature.

In the middle of this century (*Lond. Med. Gaz.*, vol. viii., p. 517, 1849), Dr. Addison observed that certain changes of pigmentation in the skin, especially in the toxic areas, viz., the distribution of the musculo-spiral and the fifth cranial pair, accompanied disease of the suprarenal bodies. Addison's observations were most accurate. Yet *pace* Dr. Samuel Wilks, Addison's disease can no longer be viewed as a pathological entity. Bronzing is not a sign of actual primary disease of the adrenals. It has followed various disorders accompanied by suppuration or sepsis. Examples are tuberculosis, cancer and caries. It accompanies the conditions like pregnancy, which load the blood with toxines. It is sometimes associated with poisoning by inorganic substances as arsenic, copper, lead and mercury. It is rather a sign that the adrenal function of filtering out unneeded colouring matters has been suspended. It

goes to build up, with other considerations, evidence that physiologically the suprarenals have ceased to exist.

Lewin, of Berlin, has noted two cases of morbus Addisonii in which the adrenals were altogether absent. In four others there was but one adrenal body to be found.

The Addisonian group of symptoms when arranged with the groups of Graves' disease, of chorea, and of rheumatic gout, presents some very interesting points of contact. The symptoms are arranged in the order of their frequency and of their pathological importance.

| Addison. | Graves. | Chorea. | Rheumatic Gout. |
|---|---|---|---|
| Pigmentation. | Tachycardia. | Tremor. | Joint Dystrophy. |
| Adynamia. | Bronchocele. | Dystrophy. | Tremor. |
| Gastro-enteric crises. | Tremor. | Tachycardia or other Neurosis. | Tachycardia. |
| | Gastro-enteric crises. | | Pigmentation. |
| Tremor. | Pigmentation. | Pallor. | Dysidrosis. |
| | Dysidrosis | | |

In an able paper on Addison's disease published some years ago by Dr. Gibbs Blake, he pointed out, on theoretic grounds, I believe, that iodine, well known as an antiseptic, is *the* remedy, *par excellence*, for suprarenal disease. I have no doubt that he was correct, and I have as little doubt that the *modus medendi* is by the annihilation of certain toxines in the circulation.

### Case 5.

*Exophthalmic Goitre, with Addisonian Bronzing.*

Patient, a man aged 36, an overseer in connection with the traffic department of a colliery. Two years previously, when in his usual health, he was much shaken and for the moment frightened, on jumping from a locomotive in motion. To this occurrence he ascribed his illness, as the palpitation came on soon afterwards, followed by bronzing of the skin.

Hitherto he had been a calm and self-possessed person, but he now grew exceedingly nervous and fidgety. Next he complained of debility, and in a short time the thyroidal enlargement made its appearance and later, the protrusion of the eyeballs. The bronzing chiefly affected the face, the neck, front of the thorax, the backs of hands, wrists and forearms. It was essentially patchy, and the dark areas were bordered by skin of normal appearance. There was no history of suppuration in any part of the body. The man had a new set of teeth at the time of his death. The illness began in 1884; and the patient died in 1891 of acute peritonitis, from perforation of a gastric ulcer. For twelve or eighteen months, previous to his death, he had suffered from symptoms of ulcer of the stomach, in addition to those belonging to Graves' disease. At the *post-mortem* examination the adrenals were found somewhat atrophied, and the left was surrounded by old adhesion.

For the capital illustration and for the details of this very interesting case, I have to thank Dr. David Drummond, of Newcastle.

Dr. Drummond has contributed a most interesting paper on this subject to *Brit. Med. Jour.*, vol. i, 1887, with details of six cases. Another reference will be made to this subject, under the heading Summary of Treatment.

M. Friedlander (Congress, Wiesbaden, vol. iv., pp. 381, 403, T. F. Bergmann, 1886), after a careful study of the phenomena of rheumatism, led especially by the symmetry of its manifestations, came to the conclusion that it is the product of intoxication of certain nerve centres. The palpitation tells us that the invasion area must include the vagal nucleus. I cannot deny that this conclusion is justified by the data. I assert farther that the very same toxines which can induce rheumatic gout are able to cause goitre in woman, Addison's disease in man and chorea in children, in whom the thymus is still active.

Chorea is a toxic invasion of the cortex. It may be viewed as a persistent suspension of the control exerted by the higher centres over mobility, clonic movement being the normal condition of ungoverned muscular tissue.

Case 5.

Thyroidal Bronzing.

A sudden and severe invasion of the centres would be interpreted as a psychosis, such as acute insanity or furious delirium. Examples are to be found in puerperal mania on the one hand—on the other, the delirium of alcoholism and of the continued fevers.

Ludwig Hirt, of Breslau, holds similar views. His words are: "All physicians recognise that there is some dim connection between St. Vitus' dance and rheumatism. The widest divergence of opinion obtains as to whether chorea is caused by rheumatism or rheumatism by chorea, or whether they are the result of one common factor. No doubt the last of these views is correct. *There is a relationship of etiology.* There is without doubt, acting in both, one common hurtful agency of an infective character. If this injurious agent exert its influence by way of the brain, chorea is the result. If, on the other hand, it acts in or on the joints, rheumatism ensues." Hirt's work on "Nervenkrankheiten," was published at Leipzig, in 1890.

My attention was not drawn to it until two years after I had put forth views in the *Journal of the Medical Sciences*, Feb., 1892, vol. xi., p. 132, nearly identical with those of Hirt. At the same time Dr. Dale made, quite independently of me, a similar suggestion in an article on "Chorea," in the *Lancet*, Nov., 1891.

That Graves' disease comes into the category of the "interchangeable neuroses" is made likely by Gildemeester's observation that epilepsy may precede goitre, and on its disappearance it may be replaced by the bronchocele. Eulenberg once witnessed Graves' disease occurring with tic and alternating with melancholia.

To return to the specialised functions of glands, we know very little with certainty, but our ideas on this profoundly interesting subject are rapidly developing. Dr. Lauder Brunton has made us familiar in this country with the fact, worked out in Padua by Lussana, in Brussels by Héger, in Geneva by Schiff and more recently in Rome by Schupfer, working under Colasanti (v. proc. of Accademia Medica di Roma, 1894), that the liver engages peptones, as

well as those poisons artificially introduced into the human stomach from without, either by accident or design.

It is possible that the thymus deals with toxines which paralyse muscle growth and repair, for the administration of the thymus gland of a sheep has been followed by improvement in pseudo-hypertrophic paralysis. (Charles Macalister, *British Medical Journal*, April 8, 1893.) This would account for the perishing of the thymus after the completion of the muscular system at maturity.

The pancreas "negotiates" superfluous glycogens, hence its paralysis involves glycosuria.[1] The lymphatic glands block the passage of protozoa and of bacilli, and when they are successful in doing this, they are styled "scrofulous" or else "cancerous" glands. At a push, the glands of the skin will do the duties of the lung, and the kidneys will take on hepatic functions.

The whole medical world has of late had its attention concentrated on the relations of the thyroid gland to cretinism on the one hand, and to the cachexia strumipriva on the other. Coming to us with the extraordinary observations of the veteran physiologist, Brown-Séquard, on the action of an entirely different material, obtained from a more remote part of the human body, the medical world has suffered from a temporary form of mania, not without parallel in recent German experience!

When the chaff of these curious proceedings has been winnowed away, some valuable contributions to practical medicine may survive.

[1] Pavy. Croonian Lectures: "On a New Departure in connection with Diabetes."—*Lancet*, July 7, 1894.

## CHAPTER III.

### Exophthalmic Goitre.

*The Disease of Basedow and Graves.*

As I pointed out in 1892, at page 44 of my work on "Septic Intoxication," the infective origin of some goitres, I am interested to observe that Dr. Greenfield, Professor of Pathology at Edinburgh University, in his Bradshaw lecture delivered before the Royal College of Physicians, London, on the 30th November (See *Lancet*, p. 1495, of December 16, 1893), is inclined to view some of the secondary phenomena of Graves' disease as possibly of auto-toxic origin.

I was amongst the first to press on the attention of the profession in this country, the infective nature of Graves' disease, which I suggested independently of S. Boinet and Silbert (*Rev. de Med.*, No. 1, 1892). My researches were commenced as early as 1871, they were written in 1891; they were published in the *Hospital Gazette* early in 1892.

Dr. Greenfield's observations are of peculiar value, they will well repay careful study. As a result of *post-mortem* examination of a series of six cases, he has shown that there is not necessarily augmented vascularity.

The essential pathology is *an increased proliferation of normal histological elements.* This may be associated at first with *heightened* functional activity. This is naturally followed by *perverted* function, and finally, by *abolished* function. And at this stage myxœdema may arise.

In two of the cases, the cervical ganglia were examined minutely. The middle cervical ganglia were the seat of

sub-acute inflammatory change. Active leucocytosis, followed by degenerative changes, was seen in the ganglion cells.

As to the medulla oblongata, the outcome of Dr. Greenfield's researches is to show that the bulbar changes are in essence:

(1) Inflammation of nerve substance.

(2) Punctate apoplexy.

(3) Degeneration of nerve cells.

These are, as Dr. Greenfield points out, the typical changes of toxic neuritis; they strongly resemble the alterations induced by tetanus and by hydrophobia.

Having considered the careful work done by Dr. Greenfield, we will next ask what is the probable explanation of the excessive growth in the histologic elements of the thyroid? Will any cause acting at one definite point explain the tremors, the paralysis of the extrinsic muscles of the eye [proptosis or exophthalmos], the paresis of control of the thyroid elements, and the arrest of vago-cardiac inhibition?

Certainly one kind of cause will do so. That is to say, any agent capable of abolishing the functions of the floor of the fourth ventricle and its correlated centres, may induce the condition known as Graves' disease.

Just as a blow may suspend the control of the gland growth and lead to that atavistic and riotous cell proliferation which we call "cancer," or as the coccidium inhibits the control of growth in the hepatic cells of a young rabbit, so various agencies, such as the toxines of pus, or of terror, may deaden the inhibitory functions which the vagus exerts over the thyroid.

Again, the same toxines of arrested katabolic process, by suspending the equilibrium control of the voluntary muscles, would give rise in mild cases to tremor, and in the more severe forms to chorea, convulsions, &c.

It is of course quite possible that instead of a centric disturbance radiating from the medulla and projected to the extremities of the vagal distribution, we might have an irritation of any one of the peripheric terminations, leading to a reflex disturbance of the centre and of the other branches.

No doubt some cases are of this nature.

Probably many of the goitres are primary disturbances in the sympathetic and in the various distributions of the pneumogastric and associated nerves.

George R. Murray, of Newcastle, embodied in a paper, contributed to the *Lancet* of Nov. 11, 1893, some points of considerable importance, which he had already brought before the notice of the Medical Society, on October 16, during the discussion on Mr. Maude's paper (see *Lancet*, Oct. 21, p. 1004; *British Medical Journal*, Oct. 21, p. 893).

This most instructive article showed that, in rabbits and in monkeys, a rise from 2° to 3° of temperature will follow a hypodermic injection of thyroidine. This suggests that the preparation depends, for its active properties, rather on the presence of extractives than on the animal alkaloids.

That goitre should have a toxic origin is by no means a novelty. By continental writers it has long been viewed as a passive septic invasion. In 1890, its infective character was suggested by Carle and Lustig (see the August number of the *Giornale di R. Accademia di Med. di Torino* for that year).

That suppuration may predispose to Graves' disease was shown by Dr. Hector Mackenzie in the same year. In the *Lancet* of Sept. 13, 1890, he noted nine cases of quinsy, out of forty cases of Graves' disease.

Jaboulay suggested, in 1891, that early goitres might be explained by the direct communication sometimes existing between the mouth and the thyroid gland, on account of a persistence of the canal of Bochdalek—the tractus thyreoglossus of His (*Proc. Med. Chirurg. Soc.*, April 10, 1894). Thus it is quite possible that congenital cases may be accounted for by direct buccal invasion as well as by the more circuitous route of lymphatic infection.

This is supported by Riviere's alleged discovery of the *cladothrix dichotoma*, an organism of the mouth, in the parenchyma of a goitre.

Rodet found many recognised, also some unnamed species of micro-organism in the substance of goitres.

Riviere notes the case of a woman in whom a goitre increased three-fold after a series of quinsies.

He quotes also the example of a woman of 40, in whom a goitre showed itself after a crop of boils on the back of the neck.

Jaboulay gives another case, that of a gardener, aged 50, who developed acute goitre after influenza. The bronchocele lasted for six months.

Riviere and Rodet made several inoculations on healthy animals with quite negative results. But this proves nothing, for we know how many persons absorb the toxines of pus for a long period of years, whilst a very small number develop a goitre. Riviere's results are embodied in a pamphlet, entitled *La Glande Thyroide et les Goitres, Anatomie Normale et Pathologique Bacteriologie* (Bailliere, Paris, 1893.)

We may take it then as highly probable that *exophthalmic goitre is a toxic neuritis of the medulla, extending at times to the pons and to the ganglia, etc., of the cervical sympathetic.*

A suggestion that the changes in the thyroid might be toxic appeared in the pages of the *Lancet.* At p. 1122 of the issue of Nov. 4, 1893, in a very able paper, Dr. George F. Johnston used the following words:—"It is quite possible that they (the symptoms of Graves' disease) are caused by the circulation in the blood of some poison which seems to be, in some respects, allied in its action to a nitrite."

That is just what some of the toxines of pus resemble. They paralyse the sympathetic and the vagal inhibition, just as the nitrite of amyl does. Dr. G. F. Johnston goes on to say, at page 1123, that, taking in health two tabloids of thyroid extract twice a day for two days, he could count on raising his pulse rate from 70 to 120. I would suggest that in obstinate cases of abnormally slow heart or bradycardia, a trial be given to thyroidine. One tablet, representing about one eighth of a gland, can be administered after each meal.

Hector Mackenzie, Cecil Beadles and Fox have observed palpitation, perspiration, headache, sleeplessness and muscular relaxation after over-doses of thyroid extract. But these are some of the symptoms of Graves' disease.

Dr. Johnston, arriving at his conclusions independently of Möbius, Byrom Bramwell and H. Williams, has shown the sharp contrast that exists between exophthalmic goitre and myxœdema in the following table :—

| Exophthalmic Goitre. | Myxœdema. |
|---|---|
| (1) *Thyroid gland* usually enlarged. | (1) Absent or atrophied. |
| (2) *Skin.* — Profuse perspiration; electrical resistance diminished. | (2) No perspiration; electrical resistance increased. |
| (3) *Subcutaneous tissue.*—Extreme emaciation in many cases. | (3) Large deposit of fat. |
| (4) *Temperature* irregular, frequently raised; feeling of warmth. | (4) Temperature lowered; feeling of chilliness. |
| (5) *Pulse* very rapid. | (5) Often very slow. |
| (6) *Mental change.*—Irritability and excitability. | (6) Hebetude and placidity. |
| (7) Often amenorrhœa. | (7) Often menorrhagia. |

But before any of these writers, Byrom Bramwell, in the "Atlas of Clinical Medicine," published in 1892, had in a foot-note drawn attention to the contrast.

It must be remembered that persistent increase in bulk of an organ by no means signifies increased functional activity. A suckling mother has enlarged breasts and there is greater functional activity, but a permanently hypertrophied breast cannot secrete milk.

That myxœdema and Graves' disease are not necessarily opposed to one another is shown by the fact that myxœdema has been said to precede Graves' disease, more frequently Graves' disease precedes myxœdema; it is doubtful if they ever really commence together. Bowles has seen three cases of co-existence. Sollier mentions one example in the *Rev. de Med.*, 1891.

## Case 6.

### *Myxœdema and Exophthalmic Goitre.*

Miss R. T. Y., aged 44, is fair, florid and tall. There is a tendency to heart disease in the family and a decidedly neurotic history. She was easily chilled as a child and all her life she has dreaded the cold.

Had post-aural abscess as an infant. At 14, had circum-anal suppuration, and at 38 suffered from axillary abscess. Had scarlatina at 15, it was probably followed by overlooked albuminuria. She thinks that the skin of the thighs has been rough ever since. Has been prone to osteo-arthritis, to vertical headache and to muco-purulent leucorrhœa ever since 18 years of age. She now has well marked Graves' disease combined with myxœdema. She is herself of opinion that the goitre preceded the myxœdematous symptoms by at least six months. It is extremely difficult to establish the precise dates of commencement of the respective diseases. But there certainly appears to be little ground for doubting that the Graves' disease existed for a long period quite unrecognised by the patient or by her friends. It must have been present at least as early as 1884.

In 1884 she began to lose her hair "from dandruff," and of course, this might have been the first sign of incipient myxœdema. With a view to improving the alopecia, her scalp was faradised. This greatly alarmed her and she suffered from severe palpitation. If this was the tachycardia of Graves' disease, the disorders must have commenced together, which would be very curious, and as far as our experience at present goes, quite unique. A severe mental shock occurred at Aix-les-Bains in 1886. After this the tachycardia became much more marked and manual tremors were first observed. She has been prone to gastric crises since the year 1886, these grew to be much more pronounced during 1888-9. There was at this time a rather vague history of supraclavicular bulging. Meanwhile, the thyroid was steadily enlarging, it reached its maximum in 1888, it was still very large during the summer 1893. It now (May 3, 1894) measures fourteen inches round. The isthmus and both lobes are enlarged. The left is the larger of the two; this is uncommon.

During 1890, she had a great deal of distress in the loins, opposite the body of the 4th lumbar vertebra. This greatly increased after influenza. A certain amount of pain and œdema are still present.

In January, 1892, she had an attack of influenza, which

distinctly accentuated the gravity of the myxœdema, and so modified the nutrition of the teeth that they have been a recurrent source of trouble to her ever since. The myxœdema was not really recognised till the close of 1892. She had the usual scanning speech. It was first noticed in the month of January, 1893, and became most marked in August. The memory failed and the clearness of the mind was seriously impaired. In the same year large doses of belladonna were given during twenty-eight days, without improvement in the general symptoms; from this time her vision began to fail and it has been defective ever since. The thyroid treatment was commenced on September 18, 1893. Three quarters of a raw thyroid, finely minced and mixed with brandy, was administered daily. After the fourth day it caused severe pain in the eleventh dorsal intercostals, where they meet below the navel. The digestion was thoroughly disturbed, she suffered much from flatulence, from pain in the great occipital nerves and from sleeplessness. The fluttering of the heart increased, and she became very cross and irritable. The dose was now diminished; thirty drops of Brady and Martin's thyroid juice were given once only. It was found to be too large a quantity, therefore the dose was still further diminished to ten drops, and then to five. At the end of November it had to be abandoned altogether.

During the thyroid treatment there was a decided improvement in the vigour of the mind, in the clearness of the speech, and in the state of the skin and its appendages, with the exception of the teeth.

*Present State.* — The chief symptoms now are recurrent pains in the branches of the fifth cranial pair; well-marked gastric crises; dyspnœa and tachycardia. There is distinct Graves' disease, but the signs of Graefe, Stellwag and Dalrymple are all absent. There is a true œdema over the sacral region and at the ankles. The skin is dry and furfuraceous. A considerable quantity of tartar has accumulated on the lingual aspect of the lower incisors, and a suppurative periodontitis is progressing beneath the tartar. There is general pruritus. She has osteo-arthritic changes,

chiefly in the knees and ankles, and is very sleepless. There is a diminished power of moral control, and she is prone to fits of profound dejection. She feels the cold acutely.

An analysis of the urine was made, with the following result :—Albumen, distinct trace; urea, 1·04 per cent. ; uric acid, 0·03 ; chlorine, one fourth of the normal amount ; sp. gr. 1012 ; reaction, acid.

*Commentary.*—Here is a case presenting a very complex series of pathological pictures. This lady has suffered from at least five distinct toxic invasions. Pus-products have been absorbed in various ways during the greater part of her existence. Abscesses in childhood, vaginal pyorrhœa during the whole of her sexual life, and gum suppuration since the development of myxœdema, have all contributed to the disastrous present results. Add to these the toxines of terror (deimatic from δεῖμα, *fright*) in 1884 and 1886. Then came influenza in 1892, with its own special poisons. In 1893 a fresh toxis in the form of atropism was induced. During the same year this lady received overdoses of thyroidine. We can scarcely be surprised at the profound changes which have occurred in the sympathetic and the cerebro-spinal system as the results of these severe and repeated poisonings.

The chief indications for treatment are, of course, to make the affected cavities aseptic to begin with. Then by all the means in our power to restore the skin to a normal condition. Thirdly, to support the general powers of life. Under this regime the patient is making steady progress towards recovery.

The solution of the problem of female predisposition lies probably in the following direction. Men are less exposed than women to the possibilities of invasion by purulent pelvic products. Men are less emotional than women, but acute goitre in males from intense excitement is not unknown ; there is a famous case detailed at p. 320 of the *Berliner Klinische Wochenschrift* for 1867. A young man of 22, after thirty minutes of furious satyriasis, with repeated attempts at unwelcomed congress, in the end effected his purpose. He was overcome with exhaustion due to the pro-

found mental excitement; in forty-eight hours he had well-marked goitre with proptosis. It is probable that the symptoms of Graves' disease existed before, but attention had not been drawn to them, so that they had passed unrecognised.

The greater stoicism of males is no doubt one reason why men are less prone than women to goitre; in some countries they certainly drink less water.

Just as women are more prone to myxœdema than men, so they are much more subject to Graves' disease, the causes of which probably induce in males, joint changes in place of the goitre.

It has been asserted by Barie and Joffroy that Basedow's disease is common in those who suffer from locomotor ataxy. Dr. Suckling brought before the Midland Medical Society, on February 8, 1893, the case of a woman of 42, in whom paraplegia followed the existence of Graves' disease. Having regard to the age and the sex of the patient, we may easily understand that both morbid expressions had a common origin in some overlooked pelvic trouble.

The occurrence of temporary acute goitre is very curious. A young married lady was giving a dinner-party. She naturally felt very solicitous that all should go off well. Dr. ———, one of the guests, observed that her thyroid slowly increased during dinner. The enlargement was imperceptible when the gentlemen joined the ladies in the drawing-room.

Making full allowance for the fact that the anamnesis is usually utterly unreliable, that goitre may have existed before, and that some epoch-marking shock has merely drawn attention to a previously overlooked condition, we must still admit that a great number of goitres have been undoubtedly produced by some profound emotion of the mind. Here we see that the causes of Graves' disease are essentially the causes of chorea. That is, to say, if toxines of traumatism or of mental shock, find their theatre of action in the cortex, we get chorea or some psychosis, if in the medulla, we get exophthalmic goitre or else rheumatism. Goitre has followed alarm, grief, chagrin, furious desire in the male, and forced cohabitation in women. But how do these emotions tell on the economy? They act in precisely the same way as a

physical shock does, compare the effects of sea-sickness [nautical intoxication].

In the November number of Brown-Séquard's *Archives de Physiologie* (1893) is an exceedingly suggestive article on the "Pathology of Shock," by M. H. Roger. He sums up the results of his observations in the following terms:—

"Nervous shock is the collective series of phenomena resulting from a violent excitation of the nervous system. It is characterised by a series of inhibitory acts, one only of which is constant and indispensable, namely, the arrest of metabolism. Shock is more common in proportion to the development and activity of the nervous system. Circumstances which augment the excitability of the nervous system, such as emotions, distress of mind, and the like, predispose to shock; those which diminish it, such as narcosis and hybernation, prevent its production or render it less serious and persistent. The determining causes of shock may be divided into two groups, according to whether they act like traumatisms, and poison the nervous centres directly, or whether they act indirectly through either the sensory nerves, the sensorial nerves, or the visceral distributions. From the point of view of pathological physiology, shock is characterised by a series of dynamic modifications (dynamogeny or inhibition) affecting all the tissues, viscera and secretions. The capital phenomenon is the arrest of metabolism, as a consequence of which there is a diminution in the quantity of carbonic acid gas in the venous blood, and, consecutively to this, troubles in calorification, respiration and circulation occur. The treatment consists in opposing hypothermy and in favouring the production of carbonic acid gas." (*Lancet*, November 11, 1893.) From this observation of Roger, and from the researches of Ross, we are able to understand the benefit of opiates and anæsthetics in warding off the evil effects of shock.

Quite independently of Dr. Roger, I had come to the same conclusions as he has done, as to the chemical results of the physiological mechanism of "shock." I can cordially endorse this very graphic account.

It is evident, when we apply Quinquaud's rule to this

sequence of phenomena, that at first animal alkaloids are precipitated in the nervous centres in excess; the inhibition of the heart is increased to so great an extent that the excito-motor fibres are overcome and syncope occurs.

In the second stage the reverse of all this obtains. The extractives, which, we may remember, stimulate the heat centres, paralyse the vaso-motor system and cause fever, are now in excess of the leucomaines or animal alkaloids, and the temperature steadily rises.

The active principles of thyroid juice belong to the extractive family.

The latest chemistry of the subject is the work of F. Gourlay. It was reported on March 22, 1894, in the *Journal of Physiology*, vol. ii., parts 1 and 2.

Gourlay has shown that in healthy thyroids, taken from different animals, there are no peptones, no proteoses, and no mucin. It is proverbially difficult to prove a negative. The author means, of course, that they did not exist in very appreciable quantities. There is absolutely no evidence that the thyroid gland contains a ferment which possesses the property of dissolving mucin.

There is one proteid, and this possibly is the active principle. *The thyroid contains a nucleo-albumin, peculiarly rich in phosphorus*, this has its origin probably in the colloid of the acini; it certainly has the power of producing intravascular coagulation.

We know that certain materials derived from without can induce goitre; these materials may be conveyed by water; thus, Captain Cook's sailors, on their return journey, tapped a barrel of water, and those who drank became goitrous.

Dr. Johnson saw goitre disappear in Durham gaol, after a change to pure water. (*Edinburgh Monthly Journal*, May, 1885.)

Billroth, McClelland and Saint-Lager give many similar observations.

Men are said to avoid conscription in France and Italy by resorting to certain old wells in order to get artificial goitre.

One of the Westerham doctors, practising in a district

where goitre is endemic, took me to see the family of a labouring man. For seven years they had lived at the foot of the North Downs, and during that time had drunk contaminated water. The mother and the three girls had then developed goitre, the father suffered from rheumatism. On moving to higher ground and obtaining a purer water supply, they all improved in health.

Thursfield, in a paper, entitled "The Etiology of Goitre in England," read in 1885 before the Society of Medical Officers of Health, made the ingenious suggestion that goitre is due to a diminished atmospheric pressure, and that it is aggravated by carrying weights. There is no doubt that both of these are contributory factors.

That they do not include the *causa vera* was shown by Josiah Williams, of Sheffield, in the *British Medical Journal*, October 24, 1885, who observed that every other resident in Novi Bazaar, a town of Bosnia, suffered from goitre, whilst in the next village, Semitza, on the same level with the same habits, and removed from it by one day's journey only, goitre was quite a rarity.

As the result of his observations on the relations of goitre and myxœdema, Mr. Robinson Stanhope makes the following summary.

(1) Congenital absence of the thyroid causes the worst forms of cretinism.

(2) As to congenital goitre, three-fourths of all cretins are goitrous.

(3) Atrophy of the thyroid may lead to myxœdema in childhood; seven cases of semi-cretinism began after measles.

(4) In degeneration of the thyroid, the development of myxœdema is in direct proportion to the amount of tissue lost.

(5) Atrophy of the thyroid in woman leads to the myxœdema of Ord.

(6) Extirpation of the thyroid causes the "cachexia strumipriva" of Kocher.

The induction of cretinism by the toxines of measles is an extremely interesting point. We may compare it with the production of goitre by the toxines of influenza and of paludism.

Many cases of goitre are recorded as having disappeared after the removal of nasal disease. An excellent account of these may be found in vol. ii., p. 133, of Burnett's work on "Diseases of the Nose and of the Accessory Cavities."

The cases of nasal disease, associated with goitre, were chiefly examples of hypertrophic rhinitis, but it has been known to accompany the atrophic form, I believe.

I have waded through a vast amount of goitrous literature, both Asiatic and European. I find that no class and no country enjoys a complete immunity from this widespread and most disfiguring disease. It was attributed to snow-water, till its discovery in Sumatra, where snow is an unknown quantity, rendered that view untenable. Then it was supposed that hard water was the cause, but, alas! for that theory, goitre is nearly unknown in New Zealand, which is largely constructed of magnesian limestone. In India, goitre is very common; untrue to its mountain-side distribution in Europe, it is said to follow the line of marshes in tropical climates, though many writers have denied the truth of this statement. I have shown in "Septic Intoxication," p. 45, that goitre may follow palustral fever. Recently I have seen, in a male patient from the West Indies, chorea occur as a sequela of paludism. Common to all cases is some organism or some organic poison. In the case of endemic goitre the organism is possibly protozoic, *i.e.*, animal rather than vegetable, as it follows water lines and can induce adenoid proliferation.

The organic poison acts like the nitrites in causing vaso-motor and vagal palsy. Most of the cases have had at least three causal elements present, some four. These are:

(1) Organic invasion or else autotoxis.
(2) Innutrition.
(3) Over-exertion.
(4) Shock.

But these are also the causes of chorea, of rheumatic gout, and probably of Addison's disease.

The worst cases are seen in the countries and amongst the classes, where people are compelled to over-exert themselves. Again, both the paludal cases, pp. 61 and 65, which

I have recorded, were developed on leaving the plains of South India for the hill station, Ootacamund.

Some will feel surprise that I should treat of such widely-differing diseases as endemic goitre and Graves' disease together. They certainly differ, as shown by St. Lager, who gives as the distinguishing features between the two goitres :—

| Endemic. | Sporadic. |
|---|---|
| Associated with cretinism. | Not associated with cretinism. |
| Disappears on expatriation. | Not altered by leaving the district. |
| Caries of teeth, stammering, deafness. | Associated with some embarrassment of respiration or circulation. |
| Relieved by iodine. | Rebellious to iodine, causation multiple. |
| Cause unique, "hydrotellurique." | Over-exertion. |
| | Pregnancy. |
| | Anæmia. |
| | Piles. |
| | Pelvic disease. |
| | Graves' disease. |
| | Syphilis. |

Yet whilst I fully admit the wide gulf which separates them pathologically, etiologically they are strongly allied and causation must count for much in classification.

Of the four classic signs, palpitation, proptosis, tremor and thyroid enlargement, that serve to make up Graves' disease, we may ask which is the characteristic symptom? I think most men are agreed that persistent acceleration of the heart is the typical sign. Without going to the rather ridiculous extreme of describing cases of exophthalmic goitre without any goitre, we can dismiss proptosis (with the signs of Dalrymple, von Graefe and Stellwag von Carion) as only meaning accidental paresis of the orbiculares and the recti of the eye. It is, therefore, only an epiphenomenon. I have seen it in lepers, and Seymour Sharkey has shown that it may occur in many unallied disorders. For the best account see Swanzy's last edition of "Eye Diseases." (See *Brain*, vol. xv., p. 121, for ocular signs in goitre.)

The thyroid enlargement sometimes precedes and sometimes succeeds the palpitation.

Sansom[1] has shown that tachycardia is common to a host of diseased conditions. Amongst the chief associated symptoms are :- –

(1) Affections of hearing, tinnitus, affections of nose and pharynx.
(2) Affections of sight, vertigo.
(3) Glycosuria.
(4) Sweats.
(5) Epistaxis.
(6) Menorrhagia.
(7) Headache.
(8) Fainting.
(9) Pigment changes.
(10) Diarrhœa.
(11) Dyspepsia.
(12) Graves' disease.
(13) Certain neuroses.
(14) Rheumatism.
(15) Influenza.
(16) Shock.

But it occurs at once to us that this is a strong "septic" group.

Other disorders often seen with palpitation are phthisis and chronic nephritis [T. G. Dill]; measles and syphilis [Buckland]; progressive myopia [Rayner Batten]; nasal growths [Woakes]; pelvic cellulitis [W. Pasteur]; anæmia [Stephen Mackenzie.] Cardiac arythmia is an ordinary result of poisoning with such nervines as tea and tobacco. We may take it that persistent palpitation, fine tremor and goitre form the essentials of Graves' disease. Every example of pulsating aorta that we see is a modified tachycardia; such cases differ in degree, rather than in kind, from Graves' disease proper.

There are, with regard to the tremors, described by Charcot as early as 1856, some important points. They are fine, frequent and antero-posterior in direction. They average eight to ten per second. There is no pronation

[1] *Proceedings Medical Society*, May 5, 1890.

present as in paralysis agitans. The tobacco tremor is similar in direction, but not so fine nor so frequent.

The tremors of alcoholic neuritis are coarse, less frequent, lateral in direction. As to this matter of direction of the tremors, it will be observed that the interossei may produce both kinds of tremor. De Watteville denies that there is any rule as to the direction of the trembling, though Charcot was of opinion that in the case of Basedow's disease, the individual fingers do not tremble as they do in the case of alcoholism and in general paralysis of the insane.

Too much importance must not be attached to these minute differences, until many more observations have been made. There is one clinical observation, however, that is of considerable value and significance. It is that the tremors of exophthalmic goitre are to be found all over the body, whilst the other tremors are much more confined to a definite and limited area.

I repeat that though Graves' disease and sporadic goitre differ so widely as to pathology, yet there is a strong causal nexus. Both own a toxic origin ; both have been cured by averting from the circulation a constant stream of pollution.

The chief difference in the method of production is that (*a*) Graves' disease is produced by a poison supplied from within the body—*autotoxis*; (*b*) goitre is often brought on by a poison obtained from outside the body—*heterotoxis*.

The following case of Graves' disease, arising from self-infection, intensified by the ptomaines of shock, differs in no way, either as to etiology or as to method of cure, from the example of sporadic goitre detailed as Case 10, the particulars of which may be found at p. 70.

I have similar cases scattered through my note-books; as they differ from those quoted in no important particular, their introduction is needless.

## Case 7.

*Exophthalmic Goitre and Urticaria.*

Mrs. —, age 31. For this most instructive case, a sketch of which has already appeared in the *Lancet*, I am indebted to Dr. C., who sent her to me from the south of London, on August 16, 1889.

The lady had been married two years, without any signs of motherhood.

She has had evident Graves' disease for at least six years. The right lobe was the first to become enlarged. This is the common rule.

Three years ago she suffered from pains in the lower part of the sacrum at night. After a distressing family shock, four months ago, she developed nettlerash,[1] to which she has been prone ever since. She had a smart gastro-enteric crisis six weeks ago.

This patient is bright and intelligent. The face is flushed, the vessels turgid, the superficial veins of the head and neck especially much distended.

She is very excitable, and is easily startled. About three times a month she gets a pain, which begins at the right supraorbital notch, and afterwards extends across the right temple and down behind the right ear to the neck, where it follows the course of the small occipital branch of the first cervical, and the acromial twig of the fourth. The distress disappears after a night's rest. This pain is possibly a toxic perineuritis.

The nettlerash is always worse when this pain is present, probably because they are both caused by an organic poison circulating at the time in the blood.

Her skin is tender, and it burns at night. The attacks of urticaria are worse at night and early in the morning. She then itches all over her body, but on the posterior cutaneous distribution of the spinal nerves, from the third to the nine-

[1] Dr. Duncan Bulkley, of New York, has observed the connection between goitre and urticaria.—*Chicago Journal of Nervous and Mental Diseases*, Oct., 1875.

teenth inclusive, the itching is most distressing, and over that area, urticarious weals appear.

She is sleepy after her luncheon. She suffers from noises in her head. She has only one molar tooth, but many suppurating fangs.

Dry, foul tongue. The isthmus and both lobes of the thyroid are greatly enlarged, so that the neck measures 15 inches round.

She gets a pain in her right side when she walks. She is very short-winded, and is always thirsty.

The urine is of a pale lemon colour, has free mucus, but no pus; phosphates are present in excess, and there are copious crystals of uric acid.

The chest is healthy, but undeveloped. During expiration it measures 26 inches; during inspiration 28½ inches; longest intake of air, 20 seconds. Suffers from attacks of violent palpitation, preceded by a sense of sinking; her ordinary heart rate is 128 beats per minute. Body weight is 119 lbs.

Is prone to sacral pains after exertion, fine tremors of the hands and feet. She has chondritis of the tibial heads.

The catamenia, which began at 14, and now tend to grow less free, only last three days, instead of four as they used to do. Two changes are enough for the whole time. There is very little suffering, it is chiefly post-pubic. She gets pain over her right eye and her neck aches at the same time. She also feels a pain in the loin. The site of this pain was made out to be the right quadratus lumborum muscle. She gets distended and diarrhœic during the period.

Excepting some evidence of general portal congestion, an abdominal examination yielded completely negative results till the pelvis was reached. The left ovary was tender, but not enlarged, the right large, very tender, and dislocated downwards, inwards and backwards. Womb was hyperplasic and tilted to the right. The ostium externum measured one millimeter in diameter, the cervical canal discharged muco-pus freely and bled readily on being touched. The mobility was complete, and the tubes were healthy.

I ordered rest and a celibate life. Combined current to

the neck, voltaism not to exceed two milliamperes. Careful and systematic lung development. I dressed the endometrium with iodized phenol, after immediate dilatation, carried out with complete aseptic precautions.

The patient being in the knee-elbow posture, I reduced the displaced ovarium, and packed it up with animal wool tampons soaked in a saturated glycerole of hamamelis. A hot douche was administered on removing the pads.

After the second replacement of the ovary, it showed no tendency to fall.

The foul fangs were directed to be removed, and a complete set of new teeth ordered.

Two milliamperes of labile voltaism were applied to the nape and sides of neck, using the commutator every two minutes, this current was combined with a gentle faradic stream.

Then the right vagus was stimulated through its whole course.

The electric applications occupied ten minutes at each sitting.

In three months the circumference of the neck had dropped to 13 inches. The pulse had fallen to 100, whilst the body weight had increased by 8lbs., and she could with ease inhale in such a manner that the lungs were completely filled.

The proptosis was better, the urticaria gone; she had lost her rheumatism, and looked much more calm and placid. In December she became *enceinte*.

After this time, having to put out, not only her own katabolic products, but those of her child, all her old symptoms returned. Autotoxis of the uterine centre, which is probably situated near the vagal nucleus, took place, and she miscarried after the sixth month. The uterus was rendered once more non-infective, and she again made a good recovery.

After this I heard occasionally of the progress of the case from the physician in attendance. Desirous of recent news, however, I wrote to the husband for a report and he replied to the following effect.

"December 1, 1893.

"My wife is uncommonly well. The neck gets better. Indeed the swelling is scarcely noticeable. The neck measures 13 inches, and the patient scaled 137 lbs. this evening. As you know, she does not possess an iron nerve, but the hands and feet shake very little. I suppose you heard that she presented me with a daughter last winter. The little one is now eleven months old and seems to be in good condition, if one can judge by her exclamations. When the fine weather comes I must get madam to bring the youngster to see you. For the rest I think that since the latter's arrival, her mother has been much better all round. If you want information on any particular points you will let me know."

"Yours, &c."

It is sometimes stated that the progress of Graves' disease is arrested by pregnancy. But Case 7 sufficiently shows that there is no rule of this kind. Indeed, its existence is opposed to probability. When we call to mind the physiological activity of the heart, of the pelvic organs, and of the glandular system involved in the processes of gestation; and when we add to it the burden of fœtal katabolism, which must fall largely on the mother, we can readily understand that a disease which has so large a toxic element as exophthalmic goitre is more likely to increase than diminish. The chorea of pregnancy, and the convulsions of childbed, both septic infections, point plainly to the perils which arise, especially at this epoch, from imperfect tissue-change and from impeded elimination.

We have been told that the *post-mortem* appearances seen in cases of sporadic goitre and of Graves' disease are characteristic in each case, whilst they widely differ from one another.

We have been taught that colloid accumulations are found in the former, whilst in the latter pigment cells replace the colloid matter.

This does not appear to be a fixed rule. Thus in one of

Horne's instances, p. 1216 of *Lancet*, vol. ii., 1892, colloid material was found in the thyroid of an exophthalmic patient.

As I have shown that proptosis is quite accidental and that it may accompany anything, of course this might have been a case of endemic goitre, complicated fortuitously with exophthalmos, but possessing none of the typical tachycardial symptoms.

Indeed this view is supported by the fact that in the Strassburg cases, examined in the laboratory of Recklinghausen, and under his supervision, Horne found bud-like endothelial proliferations in the small arteries only, very suggestive of invasion from without. (*Lancet*, November 26, 1892.)

It is noteworthy that Horne failed to find "colloid" in his seven fœtal cases; it was absent, too, in the very young children. It is quite possible that these were either protozoa in a modified form, the *débris* on the battlefield after a contest between micro-organisms and macrophages, or else the elaborated products of protozoa.

We know that the macrophages of the arterial endothelium of glands are the first and most vigorous of the protective phagocytes. Possibly, then, they were morbid micro-organisms undergoing digestion.

Recent observations on the coccidium of rabbits have shown that a true adenoma may be set up by the development of the actual cells of a protozoön.

It was pointed out by Gutnecht, as early as 1885, that the arterial walls are greatly altered in goitre. We may take it that his were examples of the endemic variety, for they were the actual thyroids which had been extirpated by Kocher of Berne. Gutnecht found masses of colloid material in the lumina of the blood vessels and widespread hyaline changes in their walls. Colloid was found both in the healthy and in the degenerated vessels. We have seen that Greenfield has made similar observations and has carried them farther.

With regard to endemic goitre, paludism and cancer, there are four points of contact which are well worthy of our most careful attention.

(1) All may be endemic.

(2) All follow the general line of streams[1] and of marshes.[2]

(3) They are probably best distributed by drinking water.

(4) Inoculation and cultivation are difficult and in some impossible.

Marsh fever, like syphilis, can be inoculated by intravenous injection, but it is not propagated by contagion from man to man.

Cancer has never been successfully inoculated.

E. Boinet and Silbert obtained ptomaines from the urine of a woman who had exophthalmic goitre. A solution of these was introduced into the circulation of healthy animals, setting up in them the symptoms of Graves' disease. At least, so it is stated in the *Lancet* of March 5, 1892.

### *Summary of the Physiology of the Thyroid and the Thymus Glands.*

(1) The thyroid is needful to health.

(2) The thyroid is not essential to life.

(3) Athyrea differs with age, sex and environment.

(4) Athyrea is revealed in childhood by cretinism.

(5) Athyrea is shown in adults by myxœdema.

(6) Before adult life, the thyroid secretion probably acts by neutralising the animal alkaloids which, according to Gautier and Quinquaud, impede the heart's action and cause coldness, possibly by increasing cardiac inhibition, by stimulating the thermal inhibitory centre, and by stimulating the sympathetic.

(7) When the thymus disappears, the thyroidin has also to help in the process of neutralising other katabolic products, called "extractives," which specially induce heat. This feverishness comes to pass in two ways; first, by vasomotor and vagal paresis; and, secondly, by thermocentral, inhibitory palsy.

[1] "Geological Distribution of Cancer in Females." ARTHUR HAVILAND, 1875.

[2] HERBERT SNOW denies that carcinoma has any marked predilection for watercourses. "The Geological Theory of Cancer Origin."—*Lancet*, Nov. 22, 1890.

(8) The knowledge at present in our possession tells us that the thyroid is not much concerned with blood making; it has much more to do with blood purification.

(9) The thyroid does not elaborate either mucin or colloid material, these are adventitious products.

(10) The thyroid does not necessarily destroy mucin, for cretins are not all myxœdematous; it is not like the habit of the human economy to take so roundabout a route, in order to rid itself of a waste material that could readily be eliminated locally in a variety of ways.

(11) The thymus might have as one function the breaking up of mucin and of fibrin. (See Macalister, *British Medical Journal*, April 8, 1893, p. 729.)

(12) The thyroid supplements the action of other glands, notably of the thymus.

(13) There are many kinds of enlargement of the thyroid, differing widely in their causation and character.

(14) It is probable that any poison which possesses the property of paralysing the floor of the fourth ventricle may cause goitre; I have shown that the toxines of the paludic protozoön can produce it. McAdam (see *Lancet*, Feb. 3, 1894), has given an example of the disorder set up by the influence of *la grippe*.

(15) At times, when thyroidine is being produced freely and it has nothing to do in the neutralising way, it may react injuriously on the economy, causing vasomotor palsy, palpitation, &c.

(16) *Exophthalmic goitre is a toxic neuritis of the medulla and adjacent structures.*

## Case 8.

### *Paludal Goitre.*

Some details of the following case appeared in the *Practitioner* for September, 1877:—

On April 23, 1877, I was consulted by Mrs. L. Q., aged 45, the widow of a military officer. For nineteen years she

has lived more or less in India, whence she has just returned. Her hair is light, she is of spare habit, and of medium height. The face is flushed and looks sunburnt; the eyeballs, especially the right, are very prominent, giving the patient the appearance of being half strangled. The neck is thin, the jugulars full, and the throbbing of the carotids is plainly visible. The right lobe of the thyroid is much enlarged, the left is also full, but not to so marked a degree as on the right side.

Her medical history has not been very eventful. She had chicken pox, measles and whooping cough before the age of 10. The catamenia appeared at 16, preceded by languor and fits of fainting.

She married at 26, but had no family. From 28 to 29 she suffered much from tropical diarrhœa and from marsh fever. On account of the latter, she was ordered from the plains to the Nilghiris. At the Hill Station of Ootacamund the fever left her, but it was replaced by Graves' disease. At 30 years of age she lost her husband, and growing weak and thin she came to England for a time.

Her health improving, she returned to India. In October, 1875, her age being now 43, she had rather severe uterine hæmorrhage for ten days, and from that epoch she herself dates her present illness. In her own notes of her case, she says: "From that time I have never been quite well, I have felt always tired, I have been troubled with incessant thirst and have had little appetite for my food." The next year the periodic flow finally left her, it being now the close of 1876.

During the past four or five years, there has been noted the occasional existence of piles and of vulvar *pruritus*. The memory has been distinctly impaired during the last twelve months. Although the disease had existed for at least fourteen years, it was not until July, 1876, that this patient perceived a swelling on the right side of her windpipe; soon afterwards the left eyeball was observed to be protuberant. Ere long the left lobe of the thyroid began to enlarge; this was followed by prominence of the right eye.

This curious cross method of attack of the eye and the

Case 8.
Paludal Goitre.

glands, was, I believe, first observed by Burney Yeo. It is recorded in a paper read before the Clinical Society on March 9. It will be found in the *British Medical Journal* for March 17, 1877, at p. 320, where there is a capital illustration of a right goitre with a left exophthalmos.

In his admirable summary, Dr. Yeo draws attention to the four following points:—

(1) The order of evolution of the phenomena.

(2) The occurrence of unilateral exophthalmos as well as of unilateral goitre.

(3) Coincident alopecia of cutaneous tracts adjacent to the enlarged eyeball.

(4) Important diffused phenomena, as recurrent diarrhœa, profuse perspirations and emotional excitability of the nervous system so frequently ignored.

In the illustration, the sign of Dalrymple [*Lancet*, May 26, 1849], *i.e.*, abnormal widening of the palpebral fissure, is well seen.

This sign is often erroneously described as that of Stellwag von Carion, or incomplete and infrequent nictitation. See *Medicinische Jahrbücher*, band 17-18, 1869.

In the case figured, No. 8, there was no falling of the hair over the eye. The peculiar condition of the nervous system, which characterises this disease was well-marked.

The patient was fluttered and disturbed by the approach of a stranger, and there was general muscular tremor. This was first observed in the lower extremities, in October, 1875; it was not recognised in the arms until the spring of 1876. With the exception of the œdematous legs, she is now much emaciated. Besides the failure of memory, so common after the climacteric, there are no mental nor cerebral symptoms whatever.

She has taken a desponding view of her case during the last six months, and for the same length of time has observed a progressive impairment of the vision of both eyes.

The face and neck are always flushed, the veins of the forehead especially prominent, and this prominence is not due to mere dilatation; evidently the venous walls have undergone some kind of hypertrophy. There is no photophobia. The sclerotics are yellow and injected.

The left ear feels "stuffed," but though the heart beats with great force and frequency, she never experiences any species of *tinnitus*. The neck measures eleven inches above the thyroid, and over the gland thirteen inches. The tumours in the neck can be emptied by pressure. The mouth is always dry, and in the morning "feels like a chip." There is follicular pharyngitis, and associated with it, as we so often see in the other sex, the hyper-resonant chest of emphysema. Thus she has two reasons for complaining, as she does, of a "dry, tickling cough, worse at night."

The area of superficial cardiac dulness is much increased, both vertically and laterally. It reaches from the third to the sixth rib. There is a systolic *bruit* and marked "heaving impulse." The heart beats a hundred and twenty per minute.

After animal food she gets gastralgia, which is relieved by vomiting.

Vertical liver-dulness = 4 inches. The bowels act daily, but the stools are pale and clay-like; there are occasionally violent gastro-enteric crises.

The spleen is natural.

The urine contains neither sugar nor albumen.

Besides a few scars of old cervical excoriations, the uterus and its appendages are normal in every way, so that the piles, if pelvic in origin, are at present maintained by the portal congestion.

The left arm measured six inches in circumference above the elbow, the right arm six and a half inches.

The legs are very œdematous; she cannot lift them from the ground, but has to raise them by means of the hands; they measure fifteen inches at the calf, ten at the ankle.

The skin, which, with the exception of the head and neck, is generally cold, is prone to itching. She has been subject to severe sweatings since February.

She suffers greatly from the heat. With the exception of dreaming and the cough, her nights are good. Pulse 120, respirations 25. Temperature 8.30 a.m., 99·8°; 8.30 p.m., 100°.

This patient derived great benefit from: (1) Perfect rest of mind and body; (2) The interdiction of butcher's meat and every form of alcohol; (3) Upward, firm, very slow massage, &c., applied to the legs; (4) The use of amyl nitrite.

The amyl was administered by the mouth, at first in two-drop doses. This proving too strong, it was subsequently given in doses of one-tenth of a minim. The patient persisted in the use of this remedy for three months, and obtained very considerable relief from it.

She had had belladonna without good results, before I took charge of the case.

She ultimately made a complete recovery.

## Case 9.

### *Paludal Goitre.*

Colonel R. is a fine, powerful man of 50. The only patient of this age, whom I can remember, as possessing his full tale of thirty-two perfectly sound teeth! Like the preceding patient, he had been living on the plains of Madras, before he contracted marsh fever, and was sent to the Nilghiris.

Here the ague disappeared, to be replaced by exophthalmic goitre. The vagal nucleus appears to have been paralysed by the palustral poisons, elaborated by Laveran's hæmatozoön.

The removal of atmospheric pressure from the skin, and the stimulating effect of the mountain air may have contributed to the tachycardia.

Very large doses of digitalis had been administered with most disastrous effect. The arms were rendered paretic.

At this stage, I saw the case and suspended the digitalis, when the patient steadily improved for a time.

The neck was very large, Dalrymple's sign and that of von Graefe were present.

A very curious change had occurred whilst this man was taking the digitalis. From having been a brave and capable

officer he became a perfect poltroon! He slowly perished, his end probably hastened by injudicious medication while in India.

Some interesting material on the distribution of goitre in Hindostan will be found in Davidson's work on "Hygiene and Disease in Warm Climates," collected by F. N. Macnamara, and in another work by the latter author, entitled, "Climate and Topography of Himalayan and sub-Himalayan Districts of British India, with reasons for assigning a malarious origin to Goitre and some other Diseases."

## CHAPTER IV.

### Treatment.

With regard to the treatment of the goitres, the most optimistic of men will be prepared, I think, to admit that the methods in vogue are by no means satisfactory.

I will venture to draw attention to one suggestive fact; it is that the most approved remedies for goitre are either germicidal or antitoxic. I have only to name iodine, iron, belladonna and quinine. That belladonna has antitoxic properties I cannot doubt. Witness the relief given to septic erythema of the throat and skin, in diphtheria and in scarlatina.

I have myself seen a cordon of belladonna tincture, painted round the leucocytic periphery of a rapidly advancing erysipelas, at once determine the battle between microphytes and phagocytes, in favour of the latter.

There are good grounds for supposing that when anæmia and goitre are benefited by iron, it is not by the physiological storing of iron, but by dint of its well-known antiseptic power that the chalybeate acts.

Hence, if we give iron to a patient, we should give it in good earnest and give nothing else. The patient should take massive doses, as in Dr. Charles Taylor's case, which I look upon as of sufficient importance to give in detail.

The paper is to be found at p. 636 of the *British Medical Journal* of March 21, 1891. It is entitled, "A Method of Administering Iron in Large Quantities."

"With a view of seeing how much iron an anæmic person could take, and also whether the rapidity of progress would be hastened, I determined to try on a suitable case the effect of an almost continuous administration of the perchloride of iron.

"I took a very extreme case of anæmia which presented itself in a girl of 19 years, who worked in a tailor's shop, and who had been getting gradually worse for two years.

She lay in bed, hardly able to move without causing dyspnœa, and showing lips and eyelids almost as bloodless as her cheeks. Having improved her digestive organs a little, I began to administer the iron. I placed by her side a quart bottle of a solution of the tinct. ferri perchlor. with some sp. chloroformi and a tumbler, telling her to sip at it as much as she could, day and night. This method of taking medicine she entered into with much zest, taking nearly three pints in the first twenty-four hours. The strength was gradually increased from 5 minims per ounce to 25 minims, and she continued to get through about a quart a day.

"She improved most rapidly, and before she left the hospital, which she did in four weeks, was able to busy herself in the ward for the whole day without fatigue. The amount of iron consumed in 27 days was exactly 30 ounces of the *British Pharmacopœia* tinct. ferri perchlor., and that large quantity without upsetting the stomach, or necessitating the use of any stronger purgative than a pill of aloes and nux vomica administered daily. If, on the other hand, she had taken the iron three times a day, in doses of 20 minims, the amount consumed in the same period would have been 3 ozs., 3 drachms.

"It is generally held, in the treatment of anæmia, that small doses are as efficacious as large, owing, I believe, to the fact that large doses so frequently upset the digestive tract, and so prevent absorption. Now, by the continuous method, with a tractable patient, one gets a very large amount taken, but in a very dilute form, and also the patient's stomach is able to decide when, and how much at a time, it is willing to receive."

Probably this is an example of hæmatopoietic paralysis of the sympathetic, induced by breathing the toxines of a close workshop, leading to the peculiar changes in the bone marrow which accompany septic anæmia.[1] I think that the water sipping, aiding elimination, had something to do with the cure.

[1] "On the Changes in the Bone Marrow in Pernicious Anæmia," Robert Muir, *Journal of Pathology and Bacteriology*, vol. ii., p. 354.

Following a long course of pelvic suppuration, I have seen a case of persistent eczema of the lips and hands, for the relief of which I sought in vain the aid of a great cutaneous specialist, get well in a few days under similar treatment.

I remember many years ago reading a series of experiments which went to show that the sulphate of iron is the best sewage precipitant that we possess. On theoretic grounds, therefore, the sulphate ought to be a good salt to use. There is, in the blood, about as much sulphur as iron.

There is little doubt that the valuable influence of iodide of potassium in late specific manifestations, and in chronic disease generally, is due to the bactericidal and antitoxic effect of the small quantities of iodine slowly liberated in the tissues.

I know that it has been urged that the treatment which improves goitre proper, often intensifies the symptoms of Graves' disease. Thus iodine, which has so often benefited bronchocele, has been said to lead to the development of proptosis in Basedow's disorder; but this point remains to be proved. It would require a great deal of iodine to paralyze the ocular recti. It is probably a *post hoc sed non propter*.

### *Summary of Treatment.*

1.—The first indication is certainly to forbid over exertion and excitement, to insist on a midday rest, and on free ventilation in sitting- and bedroom; also to suggest sleeping on the ground floor. If circumstances allow, send the patient to the pure air of the coast, endemic goitre being nearly unknown on the seaboard. Especially enjoin on the patient the importance of lung development, also of frequent gentle open-air exercise; riding, driving and boating are perhaps the best.

2.—Secure nutrition on a rational basis; forbid the use of alcohol and the abuse of the nervines; meat should be given cautiously on account of its proneness to produce disturbing peptones; goitre is not unknown in the herbivores, but it

never attains to any size. The gross, indiscriminate eaters, as the dog and the pig, are the most prone to well developed bronchocele. ("Die Cretinisme," Saint-Lager, p. 457, 1867.)

3.—Examine drinking water for toxic materials.

4.—Close all possible septic avenues, as sewer gas escapes, carious teeth, frontal, antral, and aural abscess, suppurating glands, gleet and muco-purulent discharges of all kinds from rectum and vagina; heal chronic ulcers, etc.

5.—As dilated stomach is, according to Bouchard, a fruitful source of self poisoning, from the absorption of putrid gases, it is important to cure this if possible, and also to relieve other forms of dyspepsia.

But above all things chronic constipation must be avoided. As purgatives cannot be relied on to void the saccules of colon, it is sometimes needful to irrigate the intestinal canal after vigorous abdominal massage, by means of the hot antiseptic douche.

I will cite an example where the removal of persistent pelvic suppuration was followed by the disappearance of a goitre, and of Addisonian bronzing at the same time.

That the toxines of pus had invaded the neighbourhood of the restiform bodies and the floor of the fourth ventricle, is evident by the coincident development of an inco-ordinate pharynx. Here it is possible that the adrenals were poisoned too, and their function abolished by ten years of absorption of pus products.

## Case 10.

### *Bronchocele with Addisonian Bronzing.*

This case also came from the southern suburbs, sent by Dr. M. Mrs. T., aged 35, has had a purulent, vaginal discharge, dating from the birth of her only child, ten years ago. Since that time she has had rheumatoid arthritis of knees, sore lip commissures, small, double, symmetrical goitre, incoördination of the muscles concerned in deglutition,

profound depression of mind, and a deeply bronzed skin, the latter being most marked in the face and hands. The *os tincæ* discharged muco-pus freely. The goitre, the pigmentation, the rheumatoid arthritis, and the mental gloom disappeared on removing the cause of the xanthorrhœa, viz., uterine cervicitis, which had led first to denudation of the cervix, then to general pelvic lymphatitis. From the lymphatics, *via* the thoracic duct, pus *débris* had been carried into the general circulation, with the result of gravely compromising the sympathetic system and the medulla. A condition closely resembling malarial poisoning had been set up. The disease began at Rochester, Lake Ontario, a district where goitre is endemic, so that we cannot be certain that this was a true sporadic case; her child is decidedly backward in development.

There is in the museum attached to St. Bartholomew's a drawing representing a case of this kind. It is labelled "Exophthalmic goitre with Addison's Disease."

Dr. A. T. Davies showed an example at a meeting of the Hunterian Society on April 22, 1891.

Mr. Cardew found abnormal increase of pigment in seventy per cent. of his cases of Graves' disease.

As early as 1862 Begbie had alluded to the pigmentary changes found in exophthalmic goitre. Trousseau remarked of one of his cases that the skin, formerly transparent, had become brown and freckled. General bronzing of the skin was noticed in a fatal case in St. Thomas' Hospital, in 1880. At the Ophthalmological Society, West and Carrington (*Trans.*, 1886), both presented a well marked case.

The symptoms of Graves' disease were conveniently arranged by Charcot in two groups, viz., primary or cardinal and secondary. I propose to adopt his grouping, adding about twenty important symptoms left out in his list, whilst omitting proptosis as a primary symptom.

PRIMARY OR CARDINAL. { Increased frequency of heart's action (asystole). Goitre. Rhythmical vibratory tremor.

SECONDARY. {

*Digestive organs.* — Vomiting, epigastric pain, diarrhœa, bulimia, sudden fits of hunger, thirst, hæmatemesis, jaundice, enlargement of solitary glands and of Peyer's patches.

*Respiratory organs.*—Cough, dyspnœa, increased frequency of respiration, hæmoptoë, epistaxis.

*Nervous system.*—Angina pectoris, neuralgia, stammering, paralysis, exophthalmos, Dalrymple's, Stellwag's, von Graefe's symptoms, peculiar form of paraplegia, dilated pupil, difficulty of convergence (Möbius), photophobia, tinnitus, convulsions, epileptiform crises, want of mental and of physical endurance, psychical modifications (emotional, etc.) irritability, restlessness and hurried feeling, sleeplessness.

*Integumentary system.* — Vitiligo, urticaria, pigmentary patches, sweatings, sensations of heat, at times a genuine rise of temperature, unilateral dysidrosis, diminished electrical resistance, "*tache cérébrale*," gray hair, baldness, local dropsy or general anasarca.

*Urinary system.*—Polyuria, albuminuria, glycosuria.

*Generative system.*—Menstrual derangements, impotence.

*General.*—Distressed expression, facial burning, anæmia, more or less profound cachexia, œdema of the lower extremities due to asystole. Dicrotic pulse and intermittent hydro-arthrosis.

}

These, then, are the symptoms to be sought for. When a complete group has been obtained, it is certainly wiser to relieve first those which are the greatest source of annoyance to the patient. For we may remember that the gravest organic changes are less distressing than some insignificant reflex disturbance or some sympathetic symptom.

As regards drug treatment a single remedy administered in unvarying dose should be allowed a well sustained trial, otherwise no real advance in our knowledge of drug action is possible. If hesitating between two medicines, preference should be given to that which will exert some influence in destroying germs and neutralising toxic material.

Dr. Woakes claims to have cured 85 per cent. of his cases with fluoric acid. (*Lancet*, March, 1881.)

Unguentum hydrargyri iodidi rubri, of the British Pharmacopœia, as a local application, is largely used in India.

## APPENDIX.

Since going to press my attention has been called to the fact that Grubé, in the *Neurol. Centralbl.*, 1894, No. 5, maintains the infective nature of Graves' disease. He narrates a rapidly fatal case in a woman aged 50. Three of her four children had died; one of convulsions, two of "nervous fever." As a girl she was said to have been anæmic. Some years ago she began to suffer from nervous abdominal pains, and during the last half-year she had had occasional asthmatic attacks, especially in the night. The patient herself attributed her illness to the shock caused by hearing that there was sugar in her urine (said to be about 9 per cent.) six weeks before her death. The asthmatic attacks became worse and a swelling appeared in her neck. The skin of her face appeared somewhat bronzed, as if by the sun. Exophthalmos was not much marked, but the signs of Stellwag and Gräfe were both present. The thyroid gland showed hypertrophy of the left lobe and isthmus. Many enlarged lymphatic glands could be felt in the neck. The heart was much dilated, but the heart sounds clear; the pulse was full, strong, and frequent (120 to 130). There was considerable dyspnœa, especially at night, so that the patient could not lie down in bed; some rhonchus. A certain amount of œdema in the legs. Urine (specific gravity 1030) showed trace of albumen and sugar two weeks after the supposed commencement of the disease. Some tremor in the upper extremities. Slight fever in the evenings. She died in about six weeks from the supposed commencement. Granting the infective nature of the disease, the infective agent may act (1) on the thyroid gland, causing pervertion of its function, which Möbius has suggested as the cause of Graves' disease, the nervous system being affected secondarily; or (2) on the thyroid

gland and the nervous system; or (3), and more probably, the infective agent or its products might act on the nervous system directly. Against the nervous theory of Graves' disease it has been urged that the symptoms do not point to one part only of the nervous system being affected; this is, however, no argument against the infective theory, for several different parts of the nervous system could be affected by a toxin, though the medulla oblongata might be especially susceptible, or its rich network of blood vessels might facilitate the working of the infective agent. The causes which are commonly invoked as starting points for Graves' disease—shock, excitement, over-exertion, &c.—can hardly be considered as of first moment, except in so far that they may weaken the body generally and render it less able to resist infection. Grubé adds that he can further adduce as arguments in favour of the infective theory of Graves' disease: (1) That the disease may supervene in cases of endemic or hereditary goitre; (2) the occurrence of swelling in lymph glands, noticed by Müller and in this case; and (3) that a hereditary character of Graves' disease has been recognised.

As a contribution to the evidence that the products of katabolism arrested by emotional influence may aid in the development of Graves' disease, I give some notes on the etiology of Graves' disease, by Dr. Paterson, of Cardiff, for which I am indebted to the *Lancet* of June 2, 1894:

"The influence of depressing emotions and prolonged bodily effort on the genesis of Graves' disease has received ample recognition. Patients not infrequently attribute the onset of their illness to grief or fright, or overstrain from some arduous exertion, and the same factor may come into play in bringing on recurrence of the malady after apparent cure. Whether these causes suffice to start the affection in the first instance is not quite clear, but there is no doubt of their power to hasten the appearance of the more prominent symptoms. This is well shown by a case at present under my care, which I may be allowed to quote, as it illustrates another point to which I shall refer later. A

girl 17 years of age, came under treatment in June of last year for enlarged tonsils. She exhibited some tremor and agitation, which increased readily on excitement. The tonsils having been removed under chloroform, two weeks later the patient presented a slight fulness of the middle lobe of the thyroid, which had just come on; prominence of the eyeballs was barely noticeable, and, according to the patient's statement, the trembling now extended to the legs. Ten days later the heart had increased in frequency, and at present all the symptoms of Graves' disease are in evidence. Inquiry elicited that for eighteen months the patient had been subject to attacks of tremor, which occasionally interfered with the power of writing, and had latterly been more frequent. The importance of tremor in the diagnosis of Graves' disease is now established, and it is obvious that that affection was developing slowly when the mental impression produced by the operation[1] precipitated its course. Exacerbations are not uncommon from the same cause, the thyroid enlarging and tremor and palpitation increasing under the influence of fear or sustained grief. I have notes of the case of a woman seen five years ago, in whom the affection was lighted up afresh by arduous nursing. It is noteworthy that, while tremor was very marked in the original attack, it did not recur on the later occasion, though enlargement of the thyroid gland was prominent. Anything that conduces to nervous depression may originate or light up an attack. Unhealthy surroundings and insufficient food are not without result. Rendu records a case brought on by large doses of iodide of potassium, and Russell Reynolds believes that atmospheric conditions, such as low temperature, diminished rainfall, and diminished sunshine, may have some significance. These facts are suggestive in relation to the view revived of late years by Möbius, that Graves' disease results from diseased activity of the thyroid gland. It seems to be generally accepted that this gland is a secreting organ which pours its juice

[1] I should like to guard the reader against attributing the result entirely to terror. I have frequently seen the narcosis of nitrous oxide induce persistent toxic results, in cases where there was no question of alarm.—E. T. B.

through the lymphatics into the general circulation. Now, physiological teaching tends to show that secretion in general is diminished or arrested by emotional states and anything that lowers nerve force. Fear paralyses the action of the salivary glands, and the mental depression and slowing of the circulation induced by prolonged grief are more likely to dry up secretion than promote it. It is true, vasomotor dilatation is determined by emotional states, but stimulation of the secretory nerves does not necessarily follow, and there may be obvious enlargement of the thyroid gland from vascular engorgement without increased secretion of thyroid juice. Prominence of the gland suggested its primary affection as the essence of Graves' disease, though there is the fact that goitre may come on with exophthalmos some months after other symptoms have set in, as the case quoted above shows; and, on the other hand, there may be enlargement of the thyroid gland long antecedent to any other departure from health. Certain facts give support to the idea that some of the symptoms, at least, may depend upon excessive secretion of the gland, and these are admirably set forth by Murray. In this relation, the tremor first noted by Charcot and the 'rapid heart' are, perhaps, the most significant. Along with other nervous disturbances they have been noticed after large doses of thyroid extract; but, on the other hand, it is known that similar symptoms follow, or are produced by, loss of the thyroid gland. Horsley established the occurrence of muscular tremor, and other nervous phenomena, as the result of thyroidectomy in monkeys; he demonstrated the rhythm of the tremor to be from eight to ten per second, which coincides with that of Graves' disease, given by Marie as from eight to nine per second. Von Eisselberg found identical symptoms in man after total extirpation of the thyroid. In fact, such symptoms constitute the 'neurotic' stage of Horsley's experiments, and this would indicate that the change in the gland, (if there is any) in Graves' disease, is in the direction of arrest or profound alteration of secretion. Much has been made of the contrast between this affection

and myxœdema; but here, again, the same experiments prove that the 'myxœdematous' condition is but a more advanced stage of the 'neurotic,' and is clinically supported by the fact that the symptoms of Graves' disease may give place to those of myxœdema. Recent opinion points to the secretion of the thyroid gland as 'preventing the development of some toxic product in the blood which poisons the system if the gland is removed." It is probable that some change takes place in the nervous system in Graves' disease, giving rise to the characteristic disturbances. In one other condition we meet also with such symptoms, viz., the climacteric period in women. There may be the same emotional state, some amount of fine tremor on occasions, and hot flushings and sweating, and Kisch has called attention to the 'rapid heart' of the grand climacteric. One is not infrequently struck with the resemblance of the nervous disorders in both conditions; they are of the 'general sort that accompany depressed nervous force in dependence upon a general innutrition,' and are referable to some change that has stamped its impress upon the nervous system."

Mr. Hurry Fenwick, writing on October 10, 1891, in the *British Medical Journal*, said as follows:—

"A year ago my colleague, Dr. Sansom, requested me to graft a sheep's thyroid into a case of myxœdema, which was then under his care in the London Hospital. In doing this I departed from the ordinary method, for I split each gland, and before I fixed it in its new position I rubbed the glairy secretion which oozed from the cut section into the subcutaneous tissue. I was greatly surprised next day to find that the patient's temperature had risen from its habitual sub-normal level to normal, and that the amount of urine had increased from 20 ounces per diem to 50 ounces. As I could not be sure that this was due to the absorption of the free secretion of the thyroid, I determined to inject thyroid juice hypodermically in the next case of myxœdema I chanced upon. Dr. Sansom soon placed another patient under my care, and my house-surgeon (Mr. Yardley Mills)

and I have carried out the hypodermic plan with very striking results.

"We are inclined to believe from work which we have done in this direction that the theory of the action of the diseased thyroid gland is incorrect, and that the state known as myxœdema depends upon a perverted renal function. We find that the thyroid juice possesses a distinct diuretic action in diseases of the kidney, though apparently it is negative in healthy persons. Before submitting our patient and results to the Clinical Society we would wish that so simple an injection might be tried, in order that rebutting or confirmatory evidence might be brought forward at the same time. We cannot find any record of the function of the thyroid juice except 'that it is quite unknown' (Landois); nor have we come across any intimation in the literature that it has been made use of as a diuretic in renal or cardiac disease, or in the treatment of myxœdema. We have lately learnt that Ewald has asserted that an emulsion of the thyroid produces toxic symptoms. We have not encountered such."

"The plan we have adopted is as follows: The urine having been measured and tested daily for a week, a sheep's thyroid, taken warm from the body of a carefully selected animal, is split, and ten drops of juice are mixed in a Koch's syringe with an equal amount of distilled water, and injected with aseptic precautions under the skin of the arm or shoulder blade. Some pain and slight swelling are sometimes complained of, but no inflammatory trouble has resulted. The urine increases in amount during the next day or the day after, and the effect in the myxœdema case continues for fourteen to twenty-one days."

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Möbius, who contributed so much to our early knowledge of the subject, wrote in the *Centralbl. fur Nervenheilkund.*, 1887.

Mr. Arthur Maude, who has done such admirable work on the subject, has given a very full bibliography of goitre generally in the July number of *Brain*, 1894. For a special set of references to the ocular symptoms see *Brain*, part lvii., vol. xv., p. 121.

Mr. Berry tells me that a good account of the distribution of goitre in Norway is to be found in the *Zeitsch. f. Klin. Med. Berlin*, 1891, xix., 194, by Johanessen.

An interesting case of angio-neurotic œdema is recorded by W. Ramsay Smith at p. 76 of the *Lancet*, July, 14, 1894.

One of the best sketches of Graves' disease in the English language is that of Hector Mackenzie, embodied in two clinical lectures, delivered at the Consumption Hospital, Brompton, and reported in the *Lancet* for September 13 and 20, 1890, pp. 545-601.

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